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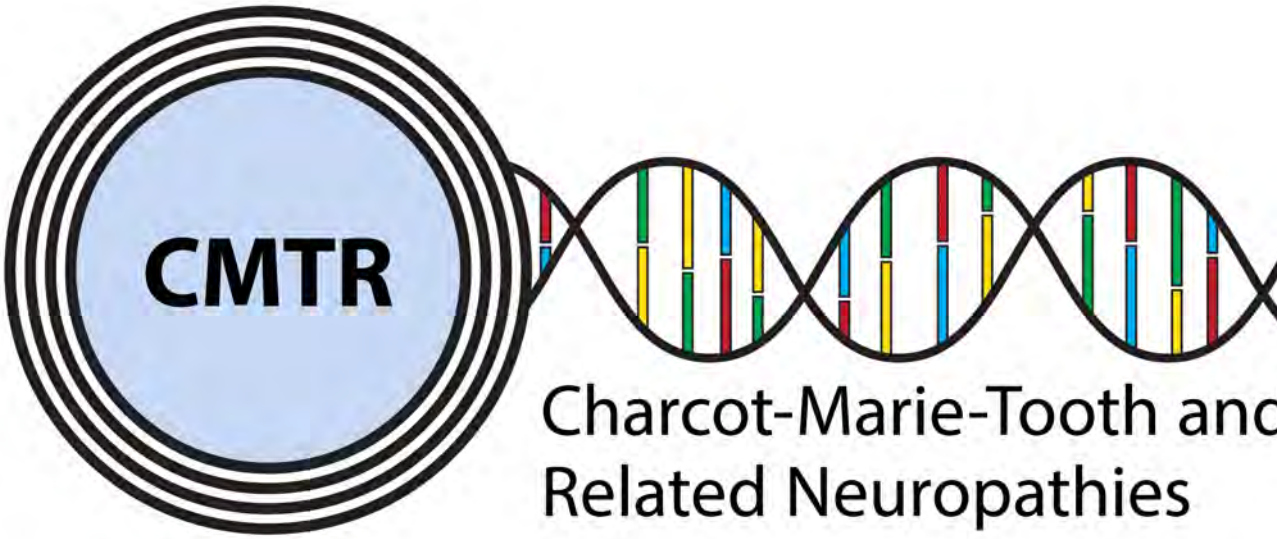
P - Poster Only, O - Oral Presentation



Charcot-Marie-Tooth and Related Neuropathies (CMTR) Abstracts

P 001 - 206

Plasma metabolites as biomarkers in Charcot-Marie-Tooth disease patients

Poster No:
P 001

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Introduction:
Charcot-Marie-Tooth disease (CMT) is the most common inherited neuropathy that lacks of therapy and of molecular markers to assess disease activity and progression. The aim of this study was to identify potential biomarkers in plasma that could inform of severity of the disease.

Methods:
Targeted plasma metabolic analysis was performed by ultrahigh performance liquid chromatography mass spectrometry (UHPLC-MS) to determine plasma levels of 33 selected metabolites in CMT patients and healthy controls. Disease severity was evaluated with CMT Neuropathy Score Version 2 (CMTNSv2). Data were analyzed using MetaboAnalyst 5.0 and SPSS.

Results:
Targeted metabolomic analysis was performed in 86 CMT patients and 75 healthy controls. Statistical tests (Fold Change Analysis and t-tests) identified one of the analysed metabolites with significant different levels. L-acetylcarnitine concentration was more than two times higher in the CMT group (median = 13.5, IQR = 8.25) compared with controls (median = 4.7, IQR = 6.86) (Mann–Whitney U test, $p < 0.001$). There was no difference in L-acetylcarnitine plasma levels between mild, moderate, and severe disease phenotype (Kruskal–Wallis H test, $p = 0.359$) and no difference between genetic CMT subtypes (Kruskal–Wallis H test, $p = 0.961$). Assessing the association between L-acetylcarnitine level and CMTNSv2, there was a weak non-significant correlation in the CMT group (Spearman correlation, $r = 0.130$, $p = 0.301$).

Conclusions:
This study shows that plasma L-acetylcarnitine level is significantly higher in CMT patients than in controls. However, there is no association between the L-acetylcarnitine concentration and disease severity of the disease. Repeated and longitudinal data assessment is needed to provide the additional information about the use of L-acetylcarnitine as a molecular CMT biomarker candidate.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Charcot-Marie-Tooth disease, Metabolome, L-acetylcarnitine

Variants and clinical features of Korean patients with *HSPB1*, *HSPB3* or *HSPB8* mutations

Poster No:
P 002

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Introduction:
Small heat shock proteins (sHSPs) are ATP-independent chaperones that help correct the folding of denatured proteins and protect cells from stress. Mutations in *HSPB1*, *HSPB8*, and *HSPB3* are implicated in inherited peripheral neuropathies (IPNs), such as Charcot-Marie-Tooth disease type 2 (CMT2) and distal hereditary motor neuropathies (dHMN).

Methods:
This study, using whole exome sequencing or targeted gene sequencing, identified 9 pathogenic or likely pathogenic variants in these three sHSP genes from 11 Korean IPN families. Clinical information included assessments of muscle atrophy, deep tendon reflex, and motor and sensory impairments. Nerve conduction studies were conducted using standard methods with surface stimulation and recording electrodes.

Results:
Most variants were located in the evolutionally well conserved crystallin domain, except for p.P182S and p.S187L in *HSPB1*. As an atypical case, a patient with dHMN2 showed two compound heterozygous variants of p.R127Q and p.Y142H in *HSPB1*, suggesting a putative case of recessive inheritance, which requires additional research to confirm. Three *HSPB8* variants were located in the p.K141 residue, which seemed to be a mutational hot spot. There were no significant differences between patient groups, which divided by sHSP genes for clinical symptoms such as onset age, severity, and nerve conduction. Early-onset patients showed a tendency of slightly decreased sensory nerve conduction values compared with late-onset patients.

Conclusions:
In this study, we have shown the genetic and phenotypic features of Korean IPN families with *HSPB1*, *HSPB3* or *HSPB8* mutations. The identified variant clinical features could be useful in the differential diagnosis of sHSP-related IPN against other forms of IPN. As a first Korean IPN cohort study examining sHSP genes, these results will, we believe, be helpful for molecular diagnosis and care of patients with CMT2 and dHMN.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Inherited peripheral neuropathies (IPNs), HSPB1, HSPB3, HSPB8, Phenotype

Genotype-phenotype correlations in Korean CMT1E families with 14 *PMP22* mutations

Poster No:
P 003

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Introduction:
Duplication and deletion of the peripheral myelin protein 22 (*PMP22*) gene cause Charcot-Marie-Tooth disease type 1A (CMT1A) and hereditary neuropathy with liability to pressure palsies (HNPP), respectively, while point mutations or small insertions and deletions (indels) usually cause CMT type 1E (CMT1E) or HNPP.

Methods:
This study was performed to identify *PMP22* mutations and to analyze the genotype–phenotype correlation in Korean CMT families. By the application of whole-exome sequencing (WES) and targeted gene panel sequencing (TS), we identified 14 pathogenic or likely pathogenic *PMP22* mutations in 21 families out of 850 CMT families who were negative for 17p12 (*PMP22*) duplication.

Results:
Most mutations were located in the well-conserved transmembrane domains. Of these, eight mutations were not reported in other populations. High frequencies of *de novo* mutations were observed, and the mutation sites of c.68C>G and c.215C>T were suggested as the mutational hotspots. Affected individuals showed an early onset-severe phenotype and late onset-mild phenotype, and more than 40% of the CMT1E patients showed hearing loss. Physical and electrophysiological symptoms of the CMT1E patients were more severely damaged than those of CMT1A while similar to CMT1B caused by *MPZ* mutations.

Conclusions:
This genetic cohort study identified 14 *PMP22* mutations in 21 Korean families as the underlying causes of CMT1E phenotypes. We carefully analyzed the genotype–phenotype correlations and compared the clinical phenotypes with other frequent CMT1 types of CMT1A and CMT1B. This study particularly provided detailed physical and electrophysiological data for all the examined patients. We believe that our results will be useful for the reference data of Koreans and the molecular diagnosis of CMT1 with or without deafness.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Charcot-Marie-Tooth disease type 1E (CMT1E), Korean, PMP22, point mutation, whole-exome sequencing

Targeting Sarm1 improves autophagic stress-induced axonal neuropathy

Poster No:
P 004

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Introduction:
Autophagy, a lysosome-dependent self-degradative process, is a critical mechanism for the clearance of misfolded proteins and dysfunctional organelles in neurons. In the peripheral nervous system, autophagic stress is associated with the development of peripheral neuropathy. However, molecular mechanism of axonal neuropathy induced by autophagic stress due to dysfunction of autophagy in peripheral neurons in vivo is still unclear.

Methods:
We employed dorsal root ganglion (DRG) neuron-specific autophagy-related gene 7 (Atg7) knockout mice using Advillin-Cre or Synapsin1-Cre recombination. We analysed the phenotypes of the mutant mice using electrophysiological, behavioural, morphological and biochemical methods. Finally we rescued the mutant phenotype with dominant negative-Sarm1 mutant.

Results:
We found that DRG neuron-specific atg7-cKO mice exhibited sensory neuropathy approximately 2 months after birth. In electron microscopic analysis, axon degeneration was clearly observed in the myelinated fibers of the sciatic nerve before the appearance of neuronal cell death. Dystrophic axons filled with abnormal vesicular accumulations and amorphous inclusions were specifically localized in the myelinated axons within the DRG in atg7-cKO mice, indicating the provocation the autophagic stress in proximal axons. In line with the EM findings, the mutant mice showed preferential induction of axonal injury-associated genes, including activating transcription factor 3, in large-size DRG neurons that constitute myelinated fibers without axotomy. Sterile alpha and TIR motif containing 1 (Sarm1), the central executioner of Wallerian degeneration, was activated in the sciatic nerves of atg7-cKO mice, and axonal degeneration and sensory neuropathy in atg7-cKO mice were prevented by Sarm1 inhibition. The axon degeneration induced by Atg7 knockdown in cultured DRG neurons was also prevented by Sarm1 inhibition.

Conclusions:
Our findings demonstrate the importance of Sarm1-dependent axon degeneration in the development of peripheral sensory neuropathy induced by impairment of autophagy.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: This study was supported by grants from the National Research Foundation of Korea (NRF; 2016R1A5A2007009, 2022R1A2C2003414). This research was supported by Korea Basic Science Institute (National research Facilities and Equipment Center) grant funded by t

Keywords: autophagy, axon degeneration, dorsal root ganglion, Sarm1

Late onset CMT2A can be a diagnostic challenge when presenting with vague sensory symptoms

Poster No:
P 005

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Introduction:
Mutations in the Mitofusion 2 gene have been reported to cause CMT2A. Mitofusion 2 is a protein that is important in mitochondrial fusion. It is well known that CMT2A can have both early onset more severe phenotypes and late onset milder phenotypes. This abstract investigates the clinical features of the late onset presentations.

Methods:
4 subjects were evaluated using clinical, laboratory, electrophysiological, and genetic data.

Results:
All four subjects presented with a diagnostic challenge given the vague sensory nature of their presentation. One presented with sharp pains in his hands, confused for carpal tunnel syndrome. Another had a sunburn sensation in her legs. The other two subjects had leg paresthesias and diffuse whole body paresthesias. All had normal routine laboratory work ups and unrevealing family histories. Two out of the four electrodiagnostic testing resulted in borderline abnormalities, which could be considered within normal limits as testing results showed very mild delayed latencies in the sural and peroneal nerves. All subjects underwent psychiatric evaluations. After extensive evaluations for all subjects, genetic testing results revealed the following: (1) a pathogenic deletion of exons 7-8 in the MFN2 gene, (2) MFN2 c.749G>A reported as a suspected mutation, (3) MFN2 c. 881G>A variant of uncertain significance and (4) MFN2 c.2119C> T pathogenic mutation. Simple interventions such as gabapentin, alpha lipoic acid and duloxetine helped control the symptoms.

Conclusions:
Late onset MFN2 mutations can present with mild vague sensory complaints that can be a diagnostic challenge, but can be treated easily if recognized.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: CMT2A, MFN2, LATE ONSET NEUROPATHY

The Effects Of PMP22 Overexpression On Endoplasmic Reticulum Stress In Charcot-Marie-Tooth disease Type 1A

Poster No:
P 006

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Introduction:
Charcot-Marie-Tooth (CMT) disease is an inherited peripheral neuropathy, affecting 1 in 2,500 people worldwide. The most common form of the disease, CMT1A, is predominantly demyelinating and is caused by a Peripheral Myelin Protein 22 (PMP22) gene duplication. PMP22 is an aggregation-prone intrinsic membrane protein of the myelin sheath mainly produced by Schwann cells (SC). It is unknown how the overexpression of PMP22 contributes to the abnormal myelin sheath structure and dysfunction as observed in CMT1A. Hence, there is no cure available to date. We hypothesize that the overexpression of PMP22 leads to an overload of the protein in the endoplasmic reticulum (ER), inducing ER stress, leading to the activation of the unfolded protein response (UPR). Therefore, we aim to investigate the effect of PMP22 overproduction and aggregation in the ER on the UPR in CMT1A Schwann cells.

Methods:
Nerve tissue and SC were isolated from wild-type (WT) and C3-PMP22 mice, an animal model for CMT1A. Furthermore, we used a new patient-in-a-dish model of CMT1A patient-derived human induced pluripotent stem cells (hiPSCs) and their isogenic controls differentiated towards Schwann cell precursors (hiPSC-SCP).

Results:
Protein ubiquitination was observed via immunostainings in primary murine C3 SC. Furthermore, the ER is more densely organized in C3 SC and CMT1A mice as observed using calnexin immunofluorescence stainings. Additionally, we confirmed a correlation between protein levels of the ER chaperone calnexin and PMP22 in CMT1A hiPSC-SCP. Lastly, ER stress sensor ratios of phosphorylated protein kinase R-like ER kinase (P-PERK)/PERK were upregulated in CMT hiPSC compared to controls.

Conclusions:
We conclude that ER stress is present in CMT1A SC and tissue as confirmed by immunofluorescence and western blot analyses. Future experiments are necessary to indicate how this affects SC myelination, providing important insights into CMT1A and other neurodegenerative, demyelinating, and PMP22-related diseases.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: Belgium, FWO (Fonds Wetenschappelijk Onderzoek)

Keywords: Charcot-Marie-Tooth disease type 1A, Schwann cells, Protein aggregation, Endoplasmic reticulum

Gene editing therapy for CMT2E via selective inactivation of common alleles

Poster No:
P 007

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Introduction:
Dominant missense mutations in NEFL cause CMT2E, while heterozygous carriers of null mutations are healthy. This suggests that inactivation of dominant alleles via CRISPR gene editing would be therapeutic. As proof-of-principle, we directly targeted NEFL-N98S with CRISPR in patient-derived induced pluripotent stem cells (iPSC) and demonstrated rescue of pathologic phenotypes in motor neurons. To expand on this strategy, we hypothesized that pairs of common polymorphisms in cis with any NEFL mutation could be targeted to inactivate disease alleles.

Methods:
We generated iPSCs from CMT2E patients with NEFL-N98S and NEFL-E396K mutations. Whole genome sequencing identified sites of heterozygous polymorphisms, which were phased with disease mutations in each iPSC line. Cas9 protein and synthetic guide RNA (gRNA) were delivered to iPSCs or neurons and gene editing was measured by targeted sequencing and droplet-digital PCR. Edited and control iPSCs were differentiated to motor neurons for gene expression and phenotypic analysis.

Results:
Three CMT2E iPSC lines were heterozygous for a haplotype block of single nucleotide polymorphisms (SNPs) flanking NEFL that could be utilized for allele-specific excision. NEFL-N98S was in phase with SNPs annotated as reference alleles, while NEFL-E396K was in phase with SNPs annotated as variant alleles. Cas9 and gRNA targeting pairs of SNPs resulted in high rates of allele-specific excision, and in some cases inversion, of the intervening sequence. Targeting reference or variant SNPs flanking the gene led to allele-specific inactivation of NEFL-N98S and NEFL-E396K, respectively. We found that excision, but not inversion, disrupted expression of the edited NEFL allele. Expression of the adjacent NEFM gene was unaffected by either outcome. We further demonstrated that allele-specific excision rescued the motor neuron disease phenotype.

Conclusions:
Common polymorphisms can be targeted with CRISPR gene editing to selectively disrupt expression of dominant disease alleles. We demonstrated the therapeutic potential of this approach in human iPSC models of CMT2E.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: NINDS R01NS119678 NIEHS U01ES032673 Charcot-Marie-Tooth Association

Keywords: Neuropathy, Gene editing, CRISPR, Neurofilaments, Motor neurons

A dose-escalation and safety study of AAVrh10-mediated cell-targeted gene replacement in a model of CMT1X demyelinating neuropathy

Poster No:
P 008

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Introduction:
X-linked Charcot-Marie-Tooth disease type 1 (CMT1X) results from mutations in GJB1 encoding the gap junction protein connexin 32 (Cx32). We showed that AAV9 carrying the human GJB1 coding sequence under the control of the human Myelin Protein Zero (MPZ) promoter rescued the neuropathy in a model of CMT1X. Here we tested different doses of an alternative AAV serotype, AAVrh10 with human MPZ promoter, in order to optimize the treatment of CMT1X neuropathy.

Methods:
We delivered by lumbar intrathecal injection the AAVrh10-MPZ-Egfp (mock) into adult wild type mice and the AAVrh10-MPZ-GJB1 (therapeutic vector) at three different doses (1x10E11, 2x10E11, and 1x10E12vg) into Gjb1-null mice, in order to evaluate biodistribution and expression of EGFP or Cx32, respectively. We then performed a dose-escalation treatment trial in randomized groups of Gjb1-null mice. Therapeutic outcome was evaluated 4 months post-injection by behavioral, electrophysiological and morphological analysis. Evaluation of toxicity and immune reactions was also performed in Gjb1-null mice injected with the standard or high AAVrh10-MPZ-GJB1 dose compared to saline.

Results:
Dose-dependent Schwann cell transduction and Cx32 expression in Gjb1-null mice was confirmed. Foot grip strength and sciatic nerve motor conduction velocities were improved in Gjb1-null mice treated with the standard or high but not with the lower dose, while nerve pathology was improved in all treatment groups compared to controls. Tissue integrity was preserved in the CNS, PNS and peripheral organs. Mild elevation of macrophages and T-cells was found only in sciatic nerves of the high dose group, but not in other neural and peripheral organ tissues, or with the standard dose. Neutralizing antibodies were induced by intrathecal delivery of AAVrh10.

Conclusions:
This study provides proof of principle for the efficacy and safety of AAVrh10-mediated GJB1 gene replacement to treat CMT1X neuropathy. Further validation of scale-up potential and safety in other species is necessary.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: Sarepta Therapeutics

Keywords: X-linked Charcot-Marie-Tooth, Gene therapy, Schwann cells, AAVrh10

Hereditary transthyretin amyloidosis (hATTR) with polyneuropathy in North Macedonia: current evidence and experiences

Poster No:
P 009

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Introduction:
Hereditary transthyretin amyloidosis (hATTR) with polyneuropathy is a rare disease due to mutations in the gene encoding transthyretin (TTR), identified by multisystem extracellular deposition of amyloid and leading to dysfunction of different organs and tissues. hATTR amyloidosis represents a diagnostic challenge for neurologists considering the wide variability in clinical presentation and multiorgan involvement.

Methods:
To highlight the recent information regarding hATTR patients in North Macedonia.

Results:
In our country, hATTR was found in 23 patients between 2017 and 2022. 1 patient has the Val33Phe mutation, while 22 patients have the Glu89Gln mutation. 12 patients are currently receiving treatment with Tafamidis, while 4 patients are on the waiting list to begin therapy for the second stage of polyneuropathy, considering the nation's Rear Disease Committee. During this time, 4 patients passed away: 2 in the second stage of polyneuropathy, 1 in the third stage of polyneuropathy, and 1 with primarily cardiac symptoms. Currently, there are 18 asymptomatic carriers who are related to symptomatic hATTR patients. According to the geographic distribution, the majority of patients originate from the eastern part of the country.

Conclusions:
hATTR amyloidosis is a severe, clinically and genetically heterogeneous, multisystem disease that affects people all over the world. In order to accelerate the earlier diagnosis and the time-sensitive treatment start, routine genetic testing is advised for patients with unexplained polyneuropathy.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: -

Keywords: amyloid, polyneuropathy, hereditary, therapy, transthyretin

Evaluation of combined RNA interference/gene replacement therapy targeting MFN2 as a potential therapeutic approach for Charcot-Marie-Tooth type 2A

Poster No:
P 010

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Introduction:
Mitofusin-2 (MFN2) is an outer mitochondrial membrane protein essential for mitochondrial networking in most cells. Autosomal dominant mutations in the MFN2 gene cause Charcot-Marie-Tooth type 2A disease (CMT2A), a severe and disabling sensory-motor neuropathy that impacts the entire nervous system. Here we propose a novel potential therapeutic approach combining RNA interference (RNAi) and gene therapy, whereby mutant and wild-type MFN2 mRNA are inhibited by RNA interference (RNAi), while the wild-type protein is restored by overexpressing cDNA encoding functional MFN2 modified to be resistant to RNAi.

Methods:
After obtaining induced pluripotent stem cells (iPSCs) from somatic cells of CMT2A patients, we targeted the MFN2 mutant allele with specific short hairpin RNAs (shRNAs) and simultaneously introduced a mutagenized MFN2 gene resistant to shRNA activity and encoding the native protein. We then differentiated iPSCs into spinal motor neurons (MNs) and analyzed the sub-cellular parameters previously found to be altered in CMT2A in vitro model to assess the impact of our therapy. We then evaluated this strategy in vivo in the MitoCharc1 CMT2A transgenic mouse model after cerebrospinal fluid (CSF) delivery of the constructs into newborn mice using adeno-associated virus 9 (AAV9).

Results:
This approach significantly rescues the CMT2A MN phenotype in vitro, stabilizing the altered axonal mitochondrial distribution and correcting abnormal mitophagic processes. This strategy also allows proper MFN2 molecular correction in CMT2A MitoCharc1 mice.

Conclusions:
Overall, our results led to a significant level of rescue of disease phenotype in CMT2A MNs, suggesting that RNAi/gene therapy combined approach might represent a promising therapeutic strategy for the broad spectrum of human diseases associated with MFN2 mutations.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: This study was funded by the Italian Ministry of Health grant GR- 2018-12365358 to FR (2018–2021) and IRCCS Foundation Ca' Granda Ospedale Maggiore Policlinico Ricerca Corrente 2020 to NB and GC. We wish to thank Progetto Mitofusina 2 Onlus and Associazio

Keywords: MFN2, RNA Interfering, gene therapy, Charcot-Marie-Tooth type 2A, induced pluripotent stem cells

Gait Kinetics and Kinematics in Distal Hereditary Motor Neuropathy, Longitudinal study

Poster No:
P 011

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Introduction:
Distal Hereditary Motor Neuropathy (DHMN) is an inherited neuromuscular disorder characterised by distal weakness. It is a disabling condition and eventually many patients need aids to walk. Research is needed to understand the muscle impairments that lead to altered gait patterns, and to develop interventions to correct walking gait conservatively. The longitudinal data presented here is aimed to ascertain relationships between muscle strength and kinetics and kinematics of gait of people with DHMN.

Methods:
Eleven people with DHMN and 9 matched controls underwent 3D Gait analysis, Isometric and Isokinetic dynamometer of hip and knee flexors/extensors, and foot plantar flexors and dorsiflexors. Measurements were repeated for DHMN participants after 6 months and 12 months. The collected data was analysed to explore the level of deterioration and to identify patterns of muscle involvement and altered gait kinetics and kinematics of people with DHMN.

Results:
• Analysis showed no significant change over 12 months in gait parameters. However, it showed an increase in the right side isokinetic dorsiflexion strength only, with 11.5 N/m (P = 0.0009). • The highest responsiveness for the right side was small for planter flexion moment and power with 0.47 and 0.42 SRM respectively. For the left side, plantar flexion moment was moderate with 0.5 SRM and small with 0.33 SRM for planter flexion power. • In comparison to controls, difference was significant in the right plantar flexion isometric and isokinetic strength with 20.9 N/m (P = 0.0023) and 20.5 N/m (P = 0.0802) respectively.

Conclusions:
We present a DHMN cohort showing ankle muscle weakness. This was associated with reduced ankle power in comparison to controls. The longitudinal study results suggest that DHMN is a slowly progressive heterogeneous group of diseases. Results also showed that 3D gait analysis is a valuable tool for research to measure gait parameters.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: DHMN, Gait analysis, Dynamometer

Differential requirement of two phosphatidylinositol 4-kinases for myelination of the Peripheral Nervous System (PNS): the cases of PI4KA and PI4KB

Poster No:
P 012

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Introduction:
Myelination of peripheral axons requires the generation and assembly of substantial amounts of plasma membrane (PM) and hence, the synthesis and transport of large amounts of membrane lipid components to the myelin sheets by surrounding Schwann cells (SCs). This process involves the production of phosphatidylinositol 4-phosphate (PI4P), a regulatory lipid required for vesicular trafficking and non-vesicular lipid transport. PI4P is synthesized by phosphatidylinositol 4-kinases (PI4Ks), of which PI4KA is located in the plasma membrane to produce PI4P that serves both as a precursor for PI(4,5)P2 and also drives phosphatidylserine (PS) transport to the PM. In contrast, PI4KB is located in the Golgi, where it controls post-Golgi vesicle transport as well as the delivery of cholesterol and ceramide from the endoplasmic reticulum to the Golgi.

Methods:
Here, we present a comparative analysis of two mouse models that we developed with targeted deletion of PI4KA (alpha-mice) or PI4KB (beta-mice) specifically in their Schwann cells.

Results:
We show that both mice display dramatic defects in peripheral myelination but their phenotypes are strikingly different. The alpha-mice are more severely affected and display much more severe motor defects than the beta-mice. Moreover, while both types show a reduction in the total lipid content of their sciatic nerves, this reduction is more severe in the alpha-mice model and affects mostly PS while the beta-mice display relatively greater reductions in phosphatidylethanolamine and sphingomyelin but not in PS. Additionally, we show that the beta-mice display a unique striking failure of SCs to engulf small nerve fibers, and a complete disintegration of the basal lamina around their Remak bundles, while alpha-mice display an almost completely opposite phenotype, with 'hyper-engulfment' of the small fibers, compared to controls.

Conclusions:
Current work is focused on understanding the molecular events that underlie these distinctive phenotypic changes, and our progress will be presented at the PNS2023 meeting.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: This work was supported by the intramural research program of the Eunice Kennedy Shriver NICHD at the NIH.

Keywords: Schwann cells, Myelination, PI4Ks, phosphoinositides

MFN2 Mutation in a Family With Overlapping Hereditary Distal Motor Sensory Neuropathy

Poster No:
P 013

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Introduction:
Charcot–Marie–Tooth disease (CMT) is the most common genetically inherited neuromuscular disorder. Type 2 CMT encompass the axonal form with more than 60 causative genes already reported. CMT2A is caused by pathogenic variants within MFN2 gene and classically presents with sensory and motor length-dependent peripheral neuropathy although clinical heterogeneity has been observed, including the presence of pyramidal features (HMSN V), optic atrophy (HMSN VI), early onset, cognitive impairment and sensory neuropathy with anydrosis. We sought to describe a family harboring a pathogenic variant in MFN2 presenting as a slowly distal motor neuropathy.

Methods:
Patients underwent neurological examination, electrophysiological study of nerve and muscle, and targeted multigene panel sequencing validated by Sanger sequencing and co-segregation analysis.

Results:
The proband presented in thirty-five years old with progressive distal weakness. His neurological examination revealed distal weakness in both upper and lower limbs, and very mild sensory abnormalities distally in lower limbs. His two daughters (aged 23 and 11) presented in their first decade of life with similar motor phenotype and normal sensory examination. Nerve conduction studies on all family members revealed the presence of preserved sensory nerve action potentials and reduced amplitude compound nerve action potentials in lower limber (> tibial nerves). Needle examination revealed acute and chronic length-dependent denervation in the lower limbs. Targeted multigene panel sequencing detected a pathogenic missense variant in the MFN2 gene (c.638T>C ; p.Ille213Thr) in the proband. This variant was validated by Sanger sequencing and co-segregation analysis confirmed that both parents were asymptomatic heterozygous carriers.

Conclusions:
We describe an uncommon clinical presentation of MFN2 gene mutation highlighting the phenotypic variability of this gene, as presented by this family presenting mainly a distal hereditary motor neuropathy (dHMN).

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: CMT2A, MFN2, dHMN, Inherited neuropathies

An exploratory study on HINT1's role in Ca2+-mediated cell signaling

Poster No:
P 014

Authors:
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Institutions:
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Introduction:
Autosomal recessive variants in the histidine triad nucleotide-binding protein 1 (HINT1) cause axonal neuropathy associated with neuromyotonia (NMAN). The clinical hallmark of NMAN is neuromyotonia, a form of nerve hyperexcitability causing delayed muscle relaxation after voluntary contraction. HINT1 is a ubiquitously expressed phosphoramidase and SUMOylase. It acts as a transcriptional inhibitor of pro-oncogenic transcription factors and as an adaptor protein of the endocannabinoid signaling pathway in the central nervous system (CNS). In the CNS, HINT1 interacts with a plethora of Ca2+ receptors (NMDAR, MOR), and cationic channels (TRPA1, TRPV2, TRPM8). Moreover, HINT1 deficiency in mice dysregulates the store-operated calcium entry pathway. Overall, it suggests that HINT1 is involved in the modulation of different Ca2+-transports systems in neurons. Yet, its function in the peripheral nerves is uncharacterized.

Methods:
We created HeLa cell lines deficient for HINT1 using CRISPR/Cas9 genome editing and studied their transcriptome profile. Gene ontology and pathway analyses revealed intracellular signaling within the most significantly affected pathways. Since HINT1 has known functions related to Ca2+-mediated signaling, we started an exploratory study on HINT1 deficient cells. We monitored Ca2+-mobilization upon different cellular stimuli using fluorescent Ca2+-indicators.

Results:
Preliminary results showed that HINT1 KO cell lines displayed higher sensitivity to ATP-evoked IP3 receptor (IP3R)-mediated calcium release compared to the WT lines. We also measured the content of the stored Ca2+ and observed no significant differences. We are currently expanding this study to other Ca2+-mediated signaling pathways to discern the specificity of HINT1's role in the many Ca2+-transport systems. Ultimately, we will test how HINT1 CMT variants interfere with these pathways and contribute to NMAN.

Conclusions:
The results of this study will provide a comprehensive and systematic study of HINT1's function as a Ca2+-signaling modulator and uncover a potential pathomechanism for NMAN.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Charcot Marie Tooth disease, Calcium Dynamics, HINT1, Mammalian cells, Neuromyotonia

Clinical Features of NOTCH2NLC-related Peripheral Neuropathies in a Japanese Cohort

Poster No:
P 015

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Introduction:
n 2019, GGC repeat expansion of the NOTCH2NLC gene was found causative for a neurodegenerative disorder, neuronal inclusion body disease (NIID), clinically characterized by various combinations of symptoms, including dementia, Parkinsonism, tremor, ataxia, seizure, peripheral neuropathy, and dysautonomia. In this study, we aim to identify abnormal repeat expansion within the NOTCH2NLC gene in a Japanese nationwide cohort of inherited peripheral neuropathy (IPN)/Charcot-Marie-Tooth disease (CMT).

Methods:
Among 2692 patients clinically diagnosed with IPN/CMT, 1783 unidentified cases after gene panel and whole-exome analyses, and RFC1 screening were enrolled in this study. GGC repeat expansion in NOTCH2NLC was screened by repeat-primed PCR, and repeat size was determined using fluorescent amplicon length analysis. The cutoff of pathogenic repeat size was set to ≥60 repeats.

Results:
We identified pathogenic repeat expansion of the NOTCH2NLC gene in 26 cases from 22 families, with the repeat size ranging from 71 to 222. The age of onset was 32.7 ± 12.4 years, younger than that of the patients presenting with typical NIID phenotype. Clinically, 18 and 8 cases were classified as axonal and demyelinating subtypes, respectively. Brain MRI showed various findings, ranging from normal to mild cerebral atrophy and leukoencephalopathy. High-intensity signal in the subcortical U-fiber on DWI, which is characteristic for NIID, was observed in only one case. Skin, muscle, or nerve biopsies were performed in several cases, and nuclear inclusion bodies were identified.

Conclusions:
Detection of GGC repeat expansion in NOTCH2NLC (22/2692) can enrich the genetic spectrum of IPN/CMT, highlighting the necessity of genetic screening. The clinical findings of these patients will further our understanding of NOTCH2NLC-related phenotypes.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: Research Committee of Ataxia, Health Labour Sciences Research Grant, the Ministry of Health, Labour and Welfare, Japan (201610002B) Japan agency for Medical Research and development (AMED) (201442014A, 201442071A, 17929553) JSPS KAKENHI Grant Numbers JP18

Keywords: CMT, NOTCH2NLC

Non-invasive assessment of peripheral nerve stiffness using ultrasound shear wave elastography as possible biomarker for demyelinating neuropathies

Poster No:
P 016

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Introduction:
The objective monitoring of disease progression and response to treatment of demyelinating polyneuropathies, acquired or inherited, is challenging. Repeated demyelination and remyelination events cause changes in nerve tissue composition and architecture that are likely to affect nerve material properties, including stiffness.

Methods:
Using ultrasound shear wave elastography (SWE), we aimed to quantify the shear wave velocity of peripheral nerves, a surrogate measure of tissue stiffness, in individuals with demyelinating polyneuropathies. We further sought to explore the effects of aging, nerve region, and nerve tensile state on nerve stiffness. Measurements, undertaken in various upper and lower limb nerves, were compared between individuals with demyelinating polyneuropathies (n=10; 54.8±12.3 years; 2 Chronic inflammatory demyelinating polyneuropathy, 4 anti-MAG, 4 Charcot Marie Tooth type 1A), healthy age-matched individuals (n=10; 54.6±13.0 years), and healthy young adults (n=9; 22.3±0.7 years).

Results:
In this cross-sectional study we showed that individuals with demyelinating polyneuropathy exhibit increased nerve stiffness compared to healthy age-matched controls (estimated mean difference = 0.7 m/s, 95%CI [0.2 to 1.2]; $p = 0.002$). Our data suggest a length dependent-pattern in neuropathy-associated changes in nerve mechanical properties. In addition, median nerve stiffness was negatively correlated with motor nerve conduction velocity ($r = -0.74$, $p = 0.037$) and compound muscle action potential ($r = -0.72$, $p = 0.044$). By comparing healthy age-matched controls with healthy young adults, we further observed that aged nerves exhibited decreased stiffness (estimated mean difference = -1 m/s, 95%CI [-1.5 to -0.5]; $p < 0.0001$). This study pinpoints significant polyneuropathy- and age-associated alterations in peripheral nerve elasticity, which are magnified under nerve tensile load (positional stiffness).

Conclusions:
These preliminary findings suggest that nerve stiffness, as assessed by SWE, could be a possible non-invasive biomarker for demyelinating polyneuropathies and warrants future powered trials. Our comprehensive assessment provides a basis for the development of standardized nerve SWE protocols in neurological disorders.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Demyelinating neuropathies, Tissue Elasticity Imaging , Peripheral Nerves , Diagnostic Imaging , Ultrasonography

Health-related quality of life in children with Charcot-Marie-Tooth Disease

Poster No:
P 017

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Introduction:
Charcot-Marie-Tooth Disease (CMT) is the most common inherited neuromuscular disorder with variability of phenotype and genotype. Children with CMT have more severe disease and long-term disability more than adult. There is limited data specific to the health-related quality of life (HRQoL) in children and adolescents with CMT. This study aimed to evaluate the HRQoL of pediatric CMT and to identify factors associated with quality of life. The findings of this study will help to improve overall care in this vulnerable pediatric population.

Methods:
This is a cross-sectional study during 2017 - 2023. HRQoL was measured using the Thai version of the Pediatric Quality of Life Inventory™ 3.0 Neuromuscular Module (PedsQL™ NMM). PedsQL NMM consists of three subscales which are neuromuscular, communication and family resource aspects. The total score is 100, higher score is better quality of life. The PedsQL™ NMM was administered to CMT children aged 2-18 years and their parents.

Results:
Preliminary result, 16 pediatric CMT and their caregiver were recruited. Mean age was 12.80 ± 1.4 years. Half were male. The mean PedsQL™NMM total score was 80 ± 9.3 by child self-report, and 75 ± 8.9 by parent proxy-report. The mean score in subscales of neuromuscular, communication and family resource were 80, 75, 83 by child self-report and 75, 84, 71 by parent proxy-report respectively. Factors associated with higher score of HRQoL was ambulation. Child self-report of HRQoL score in CMT patient is higher than other neuromuscular diseases such as Spinal Muscular Atrophy and Duchenne Muscular Dystrophy which were 70 and 72 respectively.

Conclusions:
HRQoL NMM may not be specific enough to detect limitation in CMT. Pediatric CMT quality of life outcome measure will be further study due to specifically to the CMT. The tools will sensitive enough to detect the improvement when treatment for CMT is available.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: quality of life, PedQL, CMT, pediatric

What Regulates The Early Schwann Cell Injury Response?

Poster No:
P 018

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Introduction:
Myelinating and non-myelinating Schwann cells are reprogrammed after nerve injury into repair Schwann cells, specialized for promoting nerve regeneration. The entire axon distal to the injury site degenerates after a presumed latent phase, lasting 24-36 hours in the mouse. Previously it has been shown that, morphologically, Schwann cell transformation happens after this period. However, there have been few studies investigating very early (between 3-24 hours) transcriptional changes in Schwann cells after nerve injury at sites remote from the lesion. Additionally, it is unknown whether early transcriptional changes in Schwann cells are related to axon degeneration and whether they require expression of the repair Schwann cell regulator c-JUN.

Methods:
To address these questions we have used RNA-Sequencing, mouse transgenic models, and compartmentalized mouse myelinating Schwann cell-Dorsal root ganglion co-cultures.

Results:
We delineate the early injury transcriptional signature of Schwann cells. At locations remote from the injury site in the sciatic nerve, we find that the transcriptional Schwann cell injury program starts around the time of unmyelinated axon fragmentation. Injury gene expression is inhibited in situations where axon degeneration is delayed, such as in the *Sarm1* knockout mouse and Wallerian degeneration Slow (WldS) mouse. Surprisingly, this early injury programme, initially, does not require the major injury transcription factor c-JUN in Schwann cells. However, we see precocious injury gene expression in the absence of class IIa HDACs (*Hdac4/5/7* conditional knockout). Lastly, in a co-culture model, we show that the presence of Schwann cells delays axon degeneration.

Conclusions:
The early transcriptional injury response in Schwann cells is timed around the degeneration of unmyelinated axons in a mixed nerve. It requires activation of SARM1 and the axon degeneration machinery but does not require Schwann cell c-JUN. Class IIa HDACs act as a break on Schwann cell injury gene expression. Finally, the presence of Schwann cells delays axon degeneration.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: Wellcome Trust Clinical Research Career Fellowship 206634/Z/17/Z to Dr Peter Arthur-Farraj

Keywords: Repair Schwann cell, axon degeneration, SARM1, c-JUN, nerve injury

Genetic heterogeneity of CMT in a large Indian cohort

Poster No:
P 019

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Introduction:
CMT is a genetically and clinically heterogenous disorder. Numerous genes have been implicated in CMT, each with distinct phenotypes. Data on mutation profile in Indian patients is lacking.

Methods:
To study the clinical features and mutation patterns in Indian patients with CMT. A retrospective study of NGS confirmed CMT cases.

Results:
There were 110 cases of CMT. Age at onset, presentation and duration were: 1- 58.5 years (16.72 +15.38), 1-63 years (24.04+15.84), 3 months - 50 years (7.98 + 9.37). M:F=67:43. Common variants: GDAP1(n=13, Homozygous =10, heterozygous=3, novel=7; SH3TC2(n=20, homozygous=10, heterozygous=10, novel=4); MFN2 (n=13, heterozygous=all, novel=2); PMP22 (n=11, duplications= 2, deletion=1, heterozygous=8). Other genes: PRX(3), GJB1(5), GJB(1), DYNC1H1(1), NTRK1(1), SURF1(1), SLC25A46 (1), SBF2(1), SCN11A(1), SCN9A(1), SPG11(3), PLEKHG5(4), NEFL(5), NEFH(1), MTMR2(2), MME(1), MED25(2), MORC2(2), MPZ(1), NAGLU(1), NDRG(1), PKNP(1), LRSAM1(1), LITAF(1), JPH1(1), INF2(1), HSPB1(1), HSPB8(2), HK1(2), GARS(1), FIG4(1), FGD4(1), DHTKD1(4) and AARS1(2),ATP1A1(1), DNM2(2), VCP(2) YARS1(1). Family history=36; consanguinity= 32. distal LL weakness=81. Distal UL weakness=42; proximal weakness=16. Sensory loss=25; sensory ataxia=15; tremors=22; Retinitis pigmentosa (2 in PRX), optic atrophy(3, MFN2, PRX, SLC25A46), sensorineural hearing loss(5; SH3TC2, MFN2, SLC25A46), ptosis and ophthalmoparesis(total 8)(2 of SH3TC2, one of MTMR2, PLEKHG5,NAGLU,MFN2, HSPB8, AARS1), tongue fasciculations=17)(MFN2, PMP22, SH3TC2, MTMR2, DNM2, DHTKD1, MED25, LRSAM1, LITAF, PLEKHG5, PRX, DNM2). Novel variants:GDAP1(4 frameshift (c.361delG, c.497_498delAC, c.500_501delCA, c.807delA) and 3 missense variations (c.691C>T: p.Pro231Ser, c.742G>T: p.Asp248Tyr, c.818G>T:p.Arg273Leu), SH3TC2 (two frameshift (c.1096_1097delGT, p.Thr366SerfsTer5 and c.1773delG, p.Leu592TrpfsTer53) and one each of nonsense (c.1267G>T, p.Glu423Ter) and splice site (c.385+1G>A) variant) and MFN2 (c.716A>C; p.His239Pro and c.982G>A; p.Ala328Thr).

Conclusions:
This is the first Indian study describing the clinical features and mutation pattern in a cohort of genetically confirmed cases of CMT. It highlights a variety of associated clinical manifestations and diverse genetic spectrum in Indian population. Many novel variants are identified.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Charcot-Marie-Tooth, Next Generation Sequencing, India, Mutations

CMT2C and neurovascular dysfunction: In-Vitro insights from mouse and human iPSC models

Poster No:
P 020

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Introduction:
Charcot-Marie-Tooth disease type 2C (CMT2C) and forms of distal spinal muscular atrophy are caused by mutations of transient receptor potential vanilloid 4 (TRPV4). TRPV4 is a broadly expressed, cell surface-localized cation channel that is activated by a variety of environmental stimuli and plays a role in maintaining endothelial and epithelial barriers in different organs. Recent work from our laboratory indicates that TRPV4 is expressed in vascular endothelial cells (ECs) of the nervous system and that expression the CMT2C-associated TRPV4 mutation R269C in this cell type is necessary to cause motor neuron degeneration via break down of blood-neural barriers in mice.

Methods:
In an effort to understand how TRPV4 may regulate neurovascular EC junctional contacts and barrier integrity, we have isolated primary brain and spinal cord ECs from WT, R269C mutant TRPV4, and TRPV4 KO mice. In addition, we have generated neurovascular ECs from WT, R269C mutant TRPV4, and KO isogenic human iPSC cell lines.

Results:
In these cells, we demonstrated that TRPV4 protein is expressed and functional, and that the R269C mutation causes a gain-of-channel function as determined by ratiometric calcium imaging. After 10-30 minutes of pharmacological TRPV4 activation, colonies of cells show stress fiber formation and changes in junctional protein expression as evaluated by immunofluorescent staining. In confluent cell monolayers, pharmacological activation of TRPV4 reduced barrier integrity in a dose-dependent manner as measured by TEER (transendothelial electrical resistance). Pre-treatment with a TRPV4 antagonist completely blocked barrier alterations and rapidly reversed induced changes to the barrier.

Conclusions:
Together these data show that a CMT2C-associated TRPV4 mutation increases TRPV4 activity in neural vascular ECs leading to increased intracellular calcium concentrations, stress fiber formation, and reversible reductions in barrier integrity. Our work also suggests pharmacological inhibition of TRPV4 is a promising therapeutic strategy for patients with CMT2C.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: CMT2C, iPSC, Blood Brain Barrier, Endothelial Cell, Pathobiology

IMPROVED NEUROMUSCULAR JUNCTION IN R98C MPZ HETEROZYGOUS MICE TREATED WITH IFB088

Poster No:
P 021

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Introduction:
OBJECTIVE: To evaluate neuromuscular junctions (NMJ) in R98C Mpz mutant mice treated with IFB088, a specific inhibitor of Gadd34/Ppp1r15a phosphatase. BACKGROUND: The R98C mutation in myelin protein zero (MPZ) causes a severe early-onset form of Charcot-Marie-Tooth disease 1B (CMT1B) and a similar neuropathy in knock-in mice we previously demonstrated that IFB088, a specific inhibitor of the Gadd34/Ppp1r15a phosphatase, increased holding time of the mice on the accelerating rotarod, increased their grip strength and increased both motor and sensory conduction velocities. Prior studies have shown that abnormalities of the NMJ are early morphological features of rodent models of CMT. We wished to determine whether IFB088 provides neuromuscular junction (NMJ) morphological benefit in R98C MPZ mice, a model of CMT1B in which the unfolded protein response (UPR) contributes to the neuropathy.

Methods:
METHODS: We performed a detailed NMJ morphology analysis of triangularis sterni muscle in treated and vehicle treated animals. The R98C MPZ heterozygous and wild type mice were fed with IFB088 or vehicle(saline) via gavage beginning at postnatal day 30(P30), continuing through 6 months of age (P180). Mice were evaluated clinically by rotarod, physiologically by nerve conduction studies and nerve morphology studies. Morphology analysis of immunohistochemistry at NMJ was performed for studies on 4-month-old and 6-month-old animals. Stack images were taken by confocal microscopy and measured by Image J software.

Results:
RESULTS: The percentage of fully myelinated neuromuscular junctions in the triangularis sterni muscle in R98C MPZ heterozygous mice IFB088 was increased, and demyelinated segments were shorter ($P<0.05$ by T-test and ANOVA) in mice treated with IFB088 in preterminal internodes of NMJ in 6-month-old animals.

Conclusions:
CONCLUSIONS: These data, combined with prior behavioral and physiological studies demonstrate that IFB088 improves the neuropathy of R98C MPZ CMT1B mice, a model of CMT1B involving UPR activation.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Charcot-Marie-Tooth Disease (CMT), myelin protein zero (MPZ) , neuromuscular junction (NMJ), R98C, IFB088

Clinico-genetic Overlap Between Charcot Marie Tooth Disease And Anterior Horn Cell Disorders In Indian Cohort.

Poster No:
P 022

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Introduction:
Charcot Marie Tooth disease (CMT) are a heterogenous group of inherited neuropathies characterized by distal motor and sensory involvement. Anterior horn cell diseases (AHCD) affect motor neurons of spinal cord and/or cortex. There is a significant clinico-genetic overlap between CMT and AHCD due to shared pathomechanisms.

Methods:
Retrospective study done at neuromuscular quaternary centre, to study genotype – phenotype overlap between CMT and AHCD.

Results:
Of total 131 CMT cases, 24 cases(18.3%) were included with CMT and AHCD overlap. Cases were analysed based on major pathomechanisms. Axonal transport/lysosomal trafficking: NEFL(n=5) -distal upper (UL) & lower limb (LL) weakness, dystonia, axonal neuropathy (AN) and fasciculations, DYNC1H1(n=1) –proximal LL weakness with rigid spine and AN, SPG(n=2) –distal LL weakness and AN, FIG4(n=2) –pure sensory in one and demyelinating neuropathy (DN) with cerebellar ataxia in other; Protein biogenesis : AARS(n=2) –distal UL weakness with sensory/cerebellar ataxia, and AN, GARS(n=1) –distal UL and LL weakness and AN; Ribosome associated protein quality control(PQC): VCP(n=2) –proximal LL and distal UL weakness and AN; Chaperones: HSPB1(n=1) –LL distal weakness, AN, HSPB8(n=2) –LL proximal weakness with numbness and AN, DNAJB2(n=1) – distal LL weakness and AN; others: PLEKHG5(n=4) –LL proximal weakness with fasciculations and AN, DHTKD1(n=1) –progressive respiratory failure, AN with generalized fasciculations (novel presentation). Most of them had hyperactive tendon reflexes except those with gene mutations in PQC/chaperones who had diffuse hypoactive reflexes. Though most of overlap noted with motor predominant CMT, predominant sensory involvement was seen in FIG4, AARS, HSPB8. Other additional features include ptosis (AARS, HSPB8, PLEGHG5), dystonia (NEFL, FIG4, GARS), cerebellar ataxia (FIG4, AARS).

Conclusions:
Generation of spectrum of clinical phenotypes due to 'master genes' involved in key neuronal mechanisms explain this clinico-genetic overlap of CMT- AHCD and serve as potential future therapeutic targets.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Charcot Marie Tooth disease, Anterior horn cell disease, Clinico-genetic overlap

Frequency, entity and determinants of fatigue in Charcot–Marie–Tooth disease

Poster No:
P 023

Authors:
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Introduction:
We investigated the presence of fatigue and its correlations in Charcot–Marie–Tooth disease (CMT).

Methods:
We administered the Modified Fatigue Impact Scale (MFIS) to CMT patients registered to the Italian CMT Registry and a control group. A MFIS score >38 indicated abnormal fatigue. The correlation with disease severity and clinical characteristics, the Hospital Anxiety and Depression Scale and Epworth Sleepiness Scale scores, and drug use was analysed.

Results:
Data were collected from 251 CMT patients and 57 controls. MFIS total (mean ± standard deviation 32 ± 18.3, median 33), physical (18.9 ± 9.7, 20) and psychosocial (2.9 ± 2.4, 3) scores in CMT patients were significantly higher than controls. Abnormal fatigue occurred in 36% of the patients who, compared to patients with normal scores, had more severe disease (median CMT Examination Score 9 vs. 7), more frequent use of foot orthotics (22% vs. 11%), need of support for walking (21% vs. 8%), hand disability (70% vs. 52%) and positive sensory symptoms (56% vs. 36%). Patients with abnormal fatigue had significantly increased frequency of anxiety/depression/general distress, somnolence, obesity (body mass index ≥ 30) and use of anxiolytic/antidepressant or anti-inflammatory/ analgesic drugs.

Conclusions:

Fatigue is a relevant symptom in CMT. It correlated with disease severity but also with anxiety, depression, sleepiness and obesity. Therefore, management of fatigue in CMT patients must include treatment of its different generators, including general distress, sleepiness and obesity.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: CMT, Fatigue

Severe respiratory and swallowing disorders in infantile-onset multisystem neurologic, endocrine and pancreatic disease: description of two cases.

Poster No:
P 024

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Introduction:
Infantile-onset multisystem neurologic, endocrine and pancreatic disease (IMNEPD) is a rare autosomal recessive disorder caused by mutation in the PTRH2 gene. Multiple system may be affected, notably the peripheral nervous system.

Methods:
We describe the clinical, neurophysiological, radiological and histological data of two IMNEPD cases.

Results:
We report two sisters followed up to the age of 73 and 71 years old. Starting in the childhood, both presented with progressive severe distal weakness and hypoesthesia of the four limbs, sensorineural hearing loss, mixed cerebellar and proprioceptive ataxia, intellectual disability and late onset diabetes mellitus. They needed a wheelchair since the age of 30. They developed severe respiratory impairment, with a vital capacity of 35% of normal for one and 39% for the other, requiring nocturnal ventilation. The youngest one also had important swallowing disorders that caused several hospitalizations, including in intensive care, for acute respiratory failure. The abdominal CT-scan revealed a lipomatosis of the pancreas. A cerebellar predominant atrophy was present on the cerebral MRI. Neurophysiological studies revealed an extremely severe length-dependent axonal sensory-motor neuropathy. A muscle biopsy, perfomed in the youngest, showed atrophic muscle fibers, with fiber-type grouping and some mitochondrial abnormalities. The homozygous pathogenic variant c.254A>G was found in the PTRH2 gene.

Conclusions:
Our cases highlight the respiratory and swallowing disorders, not previously described to our knowledge, presence in IMNEPD patients. Because of their severity and risk of vital complication, we suggest to systematically screen those impairment in IMNEPD patients. Furthermore, the pancreatic involvement very evocative on CT-scan is a major element to evoke the diagnosis in patients presenting a severe hereditary neuropathy. Lastly, we reporte a non-previously described pathogenic variant in the PTRH2 gene.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: PTRH2, IMNEPD, Respiratory, Cerebellum

Use, tolerability, benefit and side effects of ankle-foot orthotics in CMT

Poster No:
P 025

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Introduction:
Shoe inserts, orthopedic shoes, ankle-foot orthoses (AFOs) and walking aids are important tools in the management of Charcot-Marie-Tooth disease (CMT) patients, but data about frequency of use, benefits and tolerance are scanty.

Methods:
We administered to patients of the Italian CMT Registry an online ad hoc questionnaire investigating use, complications, perceived benefit, tolerability and emotional distress of shoe inserts, orthopedic shoes, AFOs and other orthoses/aids.

Results:
We analysed answers from 266 CMT patients (136 females; mean age 47.5±12.9 yrs., range 20-77): 185/266 (70%) patients were prescribed shoe inserts (n=145, 55%), orthopedic shoes (n=68, 26%) and/or AFOs (n=87, 33%, although 19 never used them); walking aids were prescribed to 45 subjects (18%) and upper limb orthoses to 9 (4%). Concerning AFOs, Codivilla spring (41%), Peromed (23%) and Toe-off (22%) were the most frequently used. Physiatrists were the main prescribers (62% of cases), followed by orthopedicians (39%) and neurologists (27%). Among AFOs' users, 43% used it outdoor for more than half of the time. Complications were reported by 74% of AFO's users and consisted in skin reddening (69%), foot ulcerations (18%), calluses (34%), moderate-to-severe pain (60%), which led to AFO abandonment in 33-50% of the cases. Emotional distress was rated 5.5±3.5 as a mean (on a 0-10 VAS scale, 0 none), tolerability 5.9±3.2 (10 best), benefit 6.3±3.3 (10 highest).

Conclusions:
The majority of CMT patients were prescribed shoe inserts, orthopedic shoes, and/or AFOs. However, 21% never used the prescribed AFO and 57% of AFO users wore it for less than half of the time outdoors. Although perceived benefits and tolerability are rather good, there is a high rate of complications and

considerable emotional distress, which make their use problematic. The employment of personalised/customised AFOs must be encouraged. Funded by Telethon grant GUP13006.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Charcot-Marie-Tooth

Unusual phenotypes of NEFL-related Charcot-Marie-Tooth disease

Poster No:
P 027

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Introduction:
Charcot-Marie-Tooth disease is a heterogenous group of inherited neuropathies. NEFL gene mutations are rares and can be associated with different phenotypes. Here we report five cases showing different clinical presentations of CMT related to NEFL mutations.

Methods:
Five patients from two families NEFL-related CMT were identified from those attending the department of Clinical Neurophysiology in Hôpital des Spécialités of Rabat

Results:
The family N°1 is a first-degree consanguineous family with two affected males. One patient presented with walking difficulties, progressive distal greater than proximal motor impairment and distal sensory deficit with onset around the age of 4 years. In the other case, the onset was around 7-year-old manifesting as distal upper limb weakness and scapular winging followed few years later by progressive distal greater than proximal motor weakness of the legs. Neurophysiological studies showed demyelinating neuropathy in the four limbs with neuromyotonia as an additional feature. The family N°2 is a non-consanguineous one with two affected members and their maternal aunt. All the patients had an early age of onset before age 3 years and developed progressive distal greater than proximal motor and sensory deficit. The older patients currently aged 30- and 19-year-old are still ambulant after a follow up of many years. However, a marked cerebellar ataxia is an additional feature in the aunt with a spinal and brain MRI demonstrated an atrophy of the cervico-dorsal portion of the spinal cord. The neurophysiological studies were consistent with demyelinating neuropathy in all the family members. All patients carried a homozygous pathogenic mutation in the NEFL gene.

Conclusions:
NEFL-related CMT may present with a broad different phenotypes. The present cases had atypical features including upper-limb onset, cerebellar ataxia in one patient each and neuromyotonia in 2 siblings. The latter has been only reported with HINT1 mutation. Those findings expand the clinical and electrophysiological spectrum of this entity.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: CMT, NEFL mutation, Neuromyotonia, Upper-limb onset, Cerebellar ataxia

R298C LMNA mutation can cause either peripheral neuropathy or cardiomyopathy or both: a case series study

Poster No:
P 028

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Introduction:
LMNA mutations can lead to variety of disorders, collectively termed laminopathies, involving heart, adipose, nerve, bone, and skin tissues, and some premature ageing syndromes. The phenotype associated with the homozygous R298C LMNA mutation is characterized by isolated axonal sensorimotor neuropathy or Charcot-Marie-Tooth disease (CMT) without any features suggestive of cardiac disease. Still, to our knowledge, no case of combined cardiac and neurogenic features has been reported so far in relation with this mutation.

Methods:
The follow up of 2 female patients presenting with autosomal recessive axonal neuropathy allowed the identification of two families bearing homozygote lamine A/C mutations with different combinations of axonal neuropathy and cardiac involvement among the same family.

Results:
Here we report 5 patients from 2 unrelated families with a homozygous R289C mutation in the LMNA gene and marked intra-familial variability of the disease severity and the coexistence of the cardiac involvement. 3 patients had both axonal neuropathy and cardiac manifestations, mainly conduction disturbances and 1 patient had only axonal neuropathy. Interestingly, one patient had an isolated cardiomyopathy with heterozygote defect of the R289C LMNA gene.

Conclusions:
An increased number of overlapping syndromes manifest as a result of LMNA gene mutation. Here we report, for the first time, that R289C mutation in the LMNA gene can cause cardiac manifestations in addition to the well-known phenotype of axonal neuropathy. This highlights the relevance of the screening of heart involvement in individuals who present with an axonal peripheral neuropathy related to an LMNA gene defect.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: CMT, LMNA mutation, Neuropathy, Cardiomyopathy

Patient-reported symptom severity of Charcot-Marie-Tooth disease type 1A: findings from a digital real-world study

Poster No:
P 029

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Introduction:
This analysis explores the relationship between disease severity in Charcot-Marie-Tooth disease type 1A (CMT1A), and clinical variables such as demographics, symptoms, medical history, and treatment history.

Methods:
Adults with CMT1A in France, Germany, Italy, Spain, the UK, or the USA were recruited to an ongoing, international, digital study exploring the real-world impact of CMT. Data on symptom severity were collected via a bespoke single-question patient-reported outcome (PRO) instrument, administered on the study app, CMT&Me. Participants evaluated the current severity of their symptoms using four response options: none, mild, moderate, and severe. Linear regression was used to evaluate relationships between the PRO responses and a series of explanatory clinical variables.

Results:
There were 530 responses to the symptom severity survey. The regression model was statistically significant overall, indicating a good fit of the model to the data. Beta represents the coefficient in the model, showing the direction and magnitude of the effect on the PRO outcome variable. Residency in France (ß=0.2, p=0.003), Germany (ß=0.428, p<0.001), Italy (ß=0.209, p=0.012), Spain (ß=0.246, p=0.001), and the UK (ß=0.131, p=0.019) were associated with greater symptom severity when compared with the USA (reference). Diagnosis at 0-10 years (ß=0.166, p=0.005) or 11-20 years (ß=0.132, pp=0.016) was associated with greater symptom severity when compared with 31-40 years (reference). Reporting of a greater time in years from symptom onset to diagnosis (ß=0.004, p=0.006), weakness in the arms (ß=0.168, p<0.001), hearing loss (ß=0.116, p=0.013), difficulty breathing (ß=0.15, p=0.005), burning sensation (ß=0.165, p=0.001), and/or severe fatigue (ß=0.202, p<0.001) at study baseline was associated with greater subsequent symptom severity.

Conclusions:
This study evidences a range of clinical variables – including a younger age of diagnosis, and various physical symptoms – impacting on symptom severity of CMT1A disease. Further exploration of such interactions could increase understanding of disease burden and elucidate therapeutic targets.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Charcot-Marie-Tooth disease

Patient-reported severity of lower extremity + upper limb disability in Charcot-Marie-Tooth disease type 1A: findings from a digital real-world study

Poster No:
P 030

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Introduction:
This analysis explores the relationship between lower extremity/upper limb disability in Charcot-Marie-Tooth disease type 1A (CMT1A), and a range of clinical variables.

Methods:
Adults with CMT1A in the EU5 or USA were recruited to an ongoing, international, digital study exploring the real-world impact of CMT. Patient-reported outcome (PRO) data were collected via the study app, CMT&Me, on the impact of lower extremity disability (via the lower extremity functional scale; LEFS) and upper limb disability (via the abbreviated form of the disabilities of the arm, shoulder, and hand questionnaire; QuickDASH). Linear regression was used to evaluate relationships between the PRO responses and a series of explanatory clinical variables.

Results:
Residency in Germany (LEFS: ß=0.172, $p<0.001$; QuickDASH: ß=0.097, $p<0.001$) and Italy (LEFS: ß=0.173, $p<0.001$; QuickDASH: ß=0.065, $p=0.025$) were associated with greater severity of both lower extremity and upper limb disabilities when compared with the USA (reference). Beta represents the coefficient in the model, showing the direction and magnitude of the effect on the PRO outcome variable. Diagnosis age of 21 to 30 years was associated with greater severity of lower extremity disabilities (LEFS: ß=0.074, $p<0.015$), but lesser severity of upper limb disabilities (QuickDASH: ß=-0.044, $p=0.028$), when compared with diagnosis age of 31 to 40 years (reference). Reporting of hammer toes (LEFS: ß=0.112, $p<0.001$), falls (LEFS: ß=0.159, $p<0.001$), aching (LEFS: ß=0.063, $p=0.023$; QuickDASH: ß=0.076, $p<0.001$), or severe fatigue (LEFS: ß=0.237, $p<0.001$; QuickDASH: ß=0.098, $p<0.001$) were associated with greater severity in both cases. Reporting of high (LEFS: ß=-0.133, $p<0.001$) and/or flat (LEFS: ß=-0.089, $p=0.024$) arches were associated with lesser severity in both cases. Reported use of CBD oil (LEFS: ß=0.088, $p=0.016$; QuickDASH: ß=0.051, $p=0.036$) was associated with greater severity in both cases.

Conclusions:
This study evidences a range of clinical variables predicting the impact on severity of lower extremity/upper limb disability in CMT1A.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Charcot-Marie-Tooth disease

Investigating The Impact Of The CMTX3 Structural Variation On Gene Regulation in Patient Neuronal Tissue

Poster No:
P 031

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Introduction:
CMTX3 is caused by a 78 kb insertion of chromosome 8q24.3 into a non-coding region of the CMTX3 locus at chromosome Xq27.1. We hypothesize the mutation could cause CMTX3 by (1) overexpression of the partial ARHGAP39 transcript contained within the 78 kb insertion or (2) altering the spatiotemporal regulation of nearby genes. Whilst we have reported overexpression of FGF13 (located ~1.2 Mb from the insertion breakpoint) in patient lymphoblasts, the relevance of transcriptional regulation for CMTX3 disease requires studying neuronal cells. An exploratory RNA-Seq on iPSC-derived spinal motor neurons (1 patient vs 3 controls) helped prioritize candidate genes within the CMTX3 locus, including SOX3. As SOX3 and FGF13 are important for neuronal development, gene expression was assessed at multiple timepoints throughout the differentiation process.

Methods:
RNA was collected at several timepoints throughout the motor neuron differentiation protocol including neural progenitors (NPs; differentiation day 6 and 8) (n=2 patients, n=3 controls) and mature motor neurons (MNs; differentiation day 30) (n=1 patient, n=3 controls). CMTX3 candidate genes and global transcriptome analysis was performed using a custom designed NanoString panel and RNA-Seq respectively. Dysregulated genes were investigated with Western blot analysis.

Results:
NanoString analysis showed a trend of SOX3 downregulation only in CMTX3-derived NPs (day 6) compared to controls. This change was not observed at day 8. RNA-Seq confirmed SOX3 downregulation at day 6 NPs, and preliminary Western blot results are consistent with this trend. Expression of FGF13 and ARHGAP39 was unchanged.

Conclusions:
The CMTX3 insertion affects the expression of SOX3, the closest gene to the insertion breakpoint, at a particular stage of neuronal development, suggesting gene dysregulation as the pathomechanism underlying CMTX3. As a transcription factor involved in nervous system development, the temporal SOX3 gene dysregulation identified warrants further functional investigations as a candidate gene important for peripheral nerve health.

References:
No

References 1:

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References 3:

References 4:

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Keywords: iPSC, CMTX3, Gene regulation

Genetic Variability Of Hereditary Spastic Paraplegia In Serbia

Poster No:
P 032

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Introduction:
Hereditary spastic paraplegia (HSP) is a group of neurodegenerative diseases with a high genetic and clinical heterogeneity. Numerous HSP patients remain undiagnosed despite screening for known genetic causes of HSP. Therefore, identification of novel variants is needed.

Methods:
Our first study analyzed 74 Serbian adult HSP patients from 65 families using the next-generation sequencing panel of the 13 most common HSP genes (L1CAM, PLP1, ATL1, SPAST, CYP7B1, SPG7, KIF5A, SPG11, ZYFVE26, REEP1, ATP13A2, DYNC1H1, and BICD2) in combination with a copy number variation analysis for three genes (SPAST, SPG7, and SPG11). Conclusive genetic findings were established in 23 patients from 19 families (29%). In the present study, nine patients from nine families previously negative on the HSP gene panel were selected for the whole exome sequencing (WES) – cohort 1. Beside this, 44 newly diagnosed adult HSP patients from 44 families were sent to WES directly – cohort 2.

Results:
WES analysis of cohort 1 revealed a likely genetic cause in five (56%) of nine HSP families, including variants in the ETHE1, ZFYVE26, RNF170, CAPN1, and WASHC5 genes. Only the ZFYVE26 gene was in the panel. In cohort 2, possible causative variants were found in seven (16%) of 44 patients, comprising six different genes: SPAST, SPG11, WASCH5, KIF1A, KIF5A, and c9orf12. Three of these genes were not in the panel.

Conclusions:
These results expand the genetic spectrum of HSP patients in Serbia and the region with implications for molecular genetic diagnostics and future causative therapies. WES can be the first step in HSP diagnosis in clinically well selected cohorts, especially in populations with yet non-defined HSP genetic background.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: Whole exome sequencing, analysis and variant interpretation were performed at 3billion, Inc, Seoul, Republic of Korea as a part of 3billion's research funding program.

Keywords: hereditary spastic paraplegia , Genetics, Genetic variability, whole exome sequencing

Motor neuron disease clinical signs associated with sensory involvement in a atypical clinical presentation of CANVAS

Poster No:
P 033

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Introduction:
Cerebellar ataxia, neuropathy and vestibular areflexia syndrome (CANVAS) is a late-onset, slowly progressive neurological disorder usually caused by a biallelic expansion of an intronic pentanucleotide AAGGG expansion in the RFC1 gene. After the mutation was identified, the existence of clinical variability has become evident. Here we describe two cases presenting motor neuron manifestations.

Methods:
Clinical, neurophysiological and image investigations. RFC1 gene testing

Results:
The first patient, a 60-year-old woman presented a history of progressive walking difficulty leading to wheelchair restriction in a 3 years period. She also complained of diffuse fasciculations, pain and sensory loss. She also had a history of chronic cough and bladder incontinence. On examination there were diffuse fasciculations, diffuse atrophy and increased tendon jerks associated to vibration loss. Her EMG showed fasciculations, acute denervation and reinnervation. Her disease progressed fast. She became bedridden, then developed respiratory insufficiency and died. The second case, a man, with 58-year-old man reported progressive ataxia and sensory deficits since the age of 36 years old. He also complained of chronic non-productive cough since the age of 25. On examination there was sensory ataxia and distal muscle weakness and mild atrophy. Deep tendon reflexes were increased. Vibration was abnormal. Needle examination showed the presence of diffuse chronic and active denervation in all muscles assessed. Genetic testing showed a biallelic expansion of the intronic pentanucleotide AAGGG sequence in the RFC1 gene and was negative for the hexanucleotide GGGGCC sequence in C9ORF72 gene

Conclusions:
Both patients showed the classical sensory ataxia phenotype of CANVAS associated to an evident motor neuron disorder, that was clinically very important in the first patient, and mostly electrophysiological in the second. The patients we described expand the clinical manifestations of CANVAS, adding an ELA-like presentation.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: Fapesp

Keywords: CANVAS, Electrophysiology, Genetics, Motor Neuron Disease

“Mal dos pesinhos”: Analyzing Foot and Hand sudomotor dysfunction in patients with transthyretin related familial amyloid polyneuropathy (TTR-FAP)

Poster No:
P 034

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Introduction:
Transthyretin-related familial amyloidotic polyneuropathy (ATTRv-pn) is an autosomal dominant inherited sensorimotor and autonomic polyneuropathy, which if unrecognized and untreated leads to death in approximately one decade. Since the discovery and clinical use of disease-modifying treatments, it has become imperative to recognize the responders, the non-responders and disease onset, in order to optimize treatment. As in a significant number of patients small fiber neuropathy is the onset manifestation and/or the main neurological manifestation of ATTRv-pn, we proposed to use SUDOSCAN as a disease marker.

Methods:
Sudoscan is a noninvasive and non-painful method that measures electrochemical skin conductance of hands and feet. We systematically followed asymptomatic or early onset ATTRv-pn patients with SUDOSCAN at the lower limbs to check the efficacy of this method to measure small nerve function

Results:
Thirty genetically confirmed FAP patients were included in our study so far. Nine of these patients were asymptomatic at first clinical evaluation. None of them had an abnormal SUDOSCAN. Fifteen patients were on the stage 1 of the disease; 13 of them had a normal SUDOSCAN, 1 had moderate abnormality and another had a severe abnormality. Among the patients with ATTRv-pn stages 2 and 3, none had a normal or a mildly abnormal SUDOSCAN response. Abnormalities were moderate or severe.

Conclusions:
Abnormalities in the electrochemical skin conductance measured by SUDOSCAN seems to correlate well with ATTRv-pn stages. However, we expected to detect more abnormalities at the first stages of the disease. We are now following prospectively these patients to check SUDOSCAN sensitivity to detect disease progression.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Amyloidosis, Small fiber neuropathy, Sudomotor dysfunction, Familial amyloid polyneuropathy

Predictive Modeling to Define the Locus Heterogeneity of tRNA Synthetase-related Peripheral Neuropathy

Poster No:
P 035

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Introduction:
Aminoacyl-tRNA synthetases (ARSs) are ubiquitously expressed, essential enzymes that ligate amino acids to cognate tRNAs. Variants in six ARSs cause autosomal dominant, axonal peripheral neuropathy, which presents the question: how do variants in ARSs, which are essential in all tissues, lead to phenotypes restricted to the peripheral nervous system? While protein translation and the integrated stress response have been implicated downstream of neuropathy-associated ARS variants, a unifying pathological mechanism that explains the locus and allelic heterogeneity has not been identified. All six neuropathy-associated ARSs function as cytoplasmic dimers, which is consistent with a dominant-negative effect. If this is the primary disease mechanism, it would be expected that certain variants in any cytoplasmic dimeric ARS could exert a dominant-negative effect and lead to dominant neuropathy.

Methods:
We are employing a predictive modeling strategy in which we engineer missense mutations (based on conservation and localization to functional domains) in threonyl-tRNA synthetase (*TARS1*), a cytoplasmic dimeric ARS not yet implicated in neuropathy. We test variants for loss-of-function and dominant-negative effects in yeast models, and will develop *C. elegans* models of promising variants to test for neuropathy-relevant phenotypes.

Results:
We have tested seven variants to date: (1) five are loss-of-function alleles; and (2) two of these reproducibly demonstrate dominant-toxicity, consistent with a dominant-negative effect. These results deem these alleles similar to bona fide neuropathy-associated ARS alleles.

Conclusions:
Our data suggest that certain *TARS1* variants are candidates for causing peripheral neuropathy, further suggesting a common, loss-of-function mechanism for ARS-related dominant neuropathy.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: National Institute of General Medical Sciences (GM136441), Michigan Predoctoral Training in Genetics (T32GM007544)

Keywords: Neuropathy, aminoacyl-tRNA synthetase, Yeast, Mendelian Disease, C. elegans

Vestibular Impairment In Patients With Hereditary (CMT1A) And Acquired (CIDP) Peripheral Neuropathies

Poster No:
P 036

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Introduction:
This study examines the vestibulo-ocular reflex VOR characteristics in patients with Charcot-Marie-Tooth disease 1A (CMT1A) and chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) using the non-invasive video head-impulse test (vHIT).

Methods:
This case-control study was undertaken at the Neurology Clinic, Clinical Center of Serbia, 22 patients with genetically confirmed CMT1A (mean age 51.9±13.8 years) and 10 patients with CIDP (mean age 54.7±21.8 years) were recruited. Three-dimensional v-HIT was performed. VOR gain, refixation saccade prevalence and first saccade amplitude, onset latency, peak velocity and duration were examined and compared against age-matched normal controls (NC).

Results:
In CMT1A and CIDP gait imbalance was reported in 81.8% and 60% of patients, resulting in recurrent falls in 63.6% and 40% of patients, respectively. 41% of CMT1A and 50% CIDP patients had reduced VOR gain. Refixation saccade prevalence for horizontal, anterior, and posterior canals (HC, AC, PC) were 59±28, 21±19, 54±38 in CMT1A, and in 52±35, 23±20, 59±25 CIDP, and 54±28, 13±12, 54±36 in NC. First saccade onset latency was longer in HC and PC in the CMT1A and CIDP cohort compared to NC ($p<0.05$). In CMT1A VOR impairment was associated with longer disease duration, higher CMTES score and higher total ONLS score ($p<0.05$). In both groups VOR gain for PC was lower in patients with history of recurrent falls ($p<0.05$).

Conclusions:
VOR impairment and slowing of the refixation saccades is found in CMT1A and CIDP cohort. These findings may relate to demyelinating process affecting the vestibular nerves and thus the VOR pathways. VOR impairment could be an additional contributor to imbalance and falls in patients with peripheral neuropathies.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: Nil.

Keywords: vestibular impairment , vestibulo-ocular reflex, peripheral neuropathies , video head-impulse tests

A Rare Biallelic Frameshift Variant in the MME Gene Causes Late-Onset Charcot-Marie-Tooth Disease in Two Turkish Families

Poster No:
P 037

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Introduction:
Pathogenic mutations in the membrane metalloendopeptidase (MME) gene were previously shown to cause allelic disorders including autosomal recessive and dominant axonal Charcot-Marie-Tooth disease (CMT), autosomal recessive distal hereditary motor neuropathy (dHMN) and autosomal dominant spinocerebellar ataxia (SCA). Here, we report two Turkish families with late-onset axonal CMT carrying the same biallelic frameshift variant in the MME gene.

Methods:
We screened a Turkish CMT cohort with likely recessive inheritance using whole-exome sequencing after excluding PMP22 duplication/deletion and pathogenic GDAP1 mutations. Data analysis was performed using GenomeComb and the candidate variant in MME was validated using Sanger sequencing. Homozygosity mapping was performed using HOMWES. After identification, we screened the MME variant in 130 additional CMT patients of Turkish origin.

Results:
We identified three affected individuals from two families with the novel biallelic c.531del, p.Lys177Asnfs*15 variant in the MME gene. The families were seemingly unrelated, coming from different cities in the Black Sea region. Their clinical features resembled those reported in the literature with late-onset, axonal polyneuropathy with reduced/absent reflexes. The frameshift variant is predicted to cause an early stop codon possibly causing loss of MME function. The variant co-segregated with disease status and was absent from the gnomAD database, Genesis, or our in-house cohort of Turkish CMT patients. The probands from each family have homozygous regions of 53.2Mb and 87.4Mb exome-wide, however, they only share a 5Mb homozygous haplotype on chromosome 3 encompassing the MME gene.

Conclusions:
We identified a rare frameshift variant in MME as the potential cause of late-onset axonal CMT in two Turkish families sharing a small haplotype suggesting that these families are distally related. Our findings raise the possibility that this variant could be an ancient founder mutation confined to the Black Sea region that needs further targeted investigation.

References:
Yes

References 1:
Higuchi, Y., et al. (2016). Mutations in MME cause an autosomal-recessive Charcot-Marie-Tooth disease type 2. Annals of Neurology, 79(4), 659–672.

References 2:
Auer-Grumbach, M., et al. (2016). Rare Variants in MME, Encoding Metalloprotease Neprilysin, Are Linked to Late-Onset Autosomal-Dominant Axonal Polyneuropathies. American Journal of Human Genetics, 99(3), 607-623.

References 3:
Candayan, A., et al. (2021). Genetic Survey of Autosomal Recessive Peripheral Neuropathy Cases Unravels High Genetic Heterogeneity in a Turkish Cohort. Neurology Genetics, 7(5), e621.

References 4:

Grant Support: Experimental costs were covered by TUBITAK 1001 research grant (#215S883). The first author received a FEBS short-term fellowship for research mobility and obtained a postdoctoral fellowship from University of Antwerp BOF Seal of Excellence Grants (#48147

Keywords: late onset Charcot-Marie-Tooth disease, membrane metalloendopeptidase gene

Validation of serum Neurofilament light chain in hereditary transthyretin amyloidosis in real-life practice

Poster No:
P 038

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Introduction:
Neurofilament light chain (NfL) has emerged as a sensitive biomarker of neuropathy in hereditary transthyretin amyloidosis (ATTRv). However, its applicability in real-world settings, appropriate cut-off values and longitudinal changes have yet to be established.

Methods:
We performed NfL longitudinally on stored samples from presymptomatic and symptomatic individuals carrying a neuropathic ATTR variant between 2015-2022. We assessed for associations between NFL and gender, age, creatinine, eGFR, examination scores (NIS, CMTNS, MRC) and clinical stage (PND, FAP). Receiver-operating characteristics were calculated to determine NfL cut-off values. Using mixed effect models, we explored NfL changes longitudinally prior to treatment in asymptomatic, symptomatic and converters to sensory or motor neuropathy.

Results:
59 patients with varying ATTRv mutations (26=T60A, 12=V30M, 21= other [eg. G47V, V112I, S77Y, A97S]) and PND scores (0=18, 1=29, 2=9, >3=13) were studied over a maximum pre-treatment follow-up of 4.75 years. No association was identified between NfL and age, creatinine, eGFR, gender or mutation. NfL correlated with NIS (r=0.5, p=0.0014), CMTNS (r=0.56, p=0.002) and MRC scores (r=-0.57, p<0.001). Significant differences were observed in NfL between PND0 and PND2, PND3A and PND3B (all p<0.003), and PND1 and PND3B (p= 0.047). Similarly, significant differences in NfL were seen between FAP2 and FAP0 (p= 0.001) and FAP1 (p=0.03). NfL elevation >52.2pg/ml discriminates patients with PND2 or above, from PND0-1 (AUC=0.83; 95%CI 0.71-0.95; sensitivity=100%, specificity=55.5%). Irrespective of time, NfL was higher in symptomatic and motor converters, than in asymptomatic or sensory converters (all p<0.001). NfL elevation >64.5pg/ml discriminates symptomatic or motor converters from asymptomatic groups (AUC=0.95; 95%CI 0.90-0.99; sensitivity= 91.9%, specificity=88.5%). NFL elevation >89.9pg/ml discriminates symptomatic, sensory and motor converters from the asymptomatic group (AUC=0.84; 95%CI 0.77-0.91; sensitivity= 62.9%, specificity=96.2%).

Conclusions:
Our data validates the use of NfL in real-life practice to monitor disease activity and progression and provides distinct cut-off values for conversion to symptomatic disease.

References:

No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: hereditary transthyretin amyloidosis, Neurofilament light chain, Biomarkers, polyneuropathy, monitoring

Can patisiran reduce ocular transthyretin synthesis? A pilot study in of two cases

Poster No:
P 039

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Introduction:
Variant transthyretin-mediated amyloidosis (ATTRv) is a well-characterized disease affecting the neurological and cardiovascular systems. Patisiran has been approved for neurological treatment as it reduces hepatic synthesis of transthyretin (TTR). Eye involvement is a late-onset feature increasing the risk of glaucoma and cataracts in patients. The aim of this case series was to assess whether patisiran can effectively reduce TTR synthesis in such a barrier-protected organ as the eye.

Methods:
Two patisiran-treated ATTRv patients underwent serum and aqueous humor sampling to measure TTR levels detected by SDS-PAGE and immunoblotting. Serum samples were compared to a healthy control (HC), whereas aqueous humor samples were compared to non-amyloidotic subjects affected by cataracts and glaucoma.

Results:
Serum TTR levels representative of hepatic synthesis were sharply lower in treated patients if compared to the HC (-87.5% and -93.75% respectively). Aqueous humor TTR levels showed mild-to-no reduction in treated patients compared to non-amyloidotic subjects with cataracts (-34.9% and +8.1% respectively) and glaucoma (-41.1% and -2.1%).

Conclusions:
Patisiran does not seem to be so effective in inhibiting ocular TTR synthesis as it is in inhibiting hepatic synthesis. Re-engineering the envelope could allow the drug to target RPE cells thus avoiding any ocular involvement.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: amyloidosis, ATTR, ATTRv, RNA interference, transthyretin

The Silent Period for Small Fiber Sensory Neuropathy Assessment in a Mixed Cohort of Transthyretin-Mediated Amyloidosis

Poster No:
P 040

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Introduction:
Transthyretin-mediated amyloidosis (ATTR) is a rare multisystemic disease involving the peripheral nervous system and heart. Autonomic and small fiber involvement is one of the hallmarks of ATTR, and many tools have been proposed to assess this aspect. The aim of this study was to investigate cutaneous and mixed nerve silent periods (CSP and MnSP) as instruments for small fiber assessment.

Methods:
A total of 21 ATTR patients, 20 healthy controls, and 18 asymptomatic carriers underwent a sensory conduction study from the right sural and non-dominant ulnar nerves. A motor conduction study from the right deep peroneal and non-dominant ulnar nerves, with their F waves, CSPs, and MnSPs, was performed

Results:
The amplitudes of the sural and ulnar sensory nerves and of the peroneal and ulnar motor nerves were reduced in ATTR patients compared to the other groups. F waves from the ulnar and peroneal nerves showed no differences between the three groups. The CSP and MnSP latency, but not amplitude, were increased in both the ulnar and peroneal nerves of ATTR patients.

Conclusions:
ATTR patients showed axonal involvement of large sensory and motor nerve fibers and demyelinating features of small sensory fibers.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: cutaneous silent period, mixed nerve silent period, neurophysiology, transthyretin-mediated amyloidosis

Hippo Pathway in Schwann Cells and Damage Repair of Peripheral Nervous System

Poster No:
P 041

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Introduction:
Hippo pathway is an evolutionarily conserved signaling pathway consist of a series of MST/LATS kinase complexes. Its key transcriptional effectors YAP and TAZ control transcription factors such as TEAD family to direct gene expression. The regulation of Hippo pathway, especially the level change of YAP and TAZ, significantly influences the cell fate switching from proliferation to differentiation, regeneration and post-injury repair. This review highlights the main findings of Hippo pathway in development and the repair role of Schwann cells after peripheral nerve injury, summarizes other roles of Hippo pathway in damage repair of peripheral nerve system, and discuss the potential future research which probably contribute to novel therapeutic strategies.

Methods:
We will discuss Hippo pathway in the two major parts. Firstly, we will introduce Hippo pathway in PNS development from neural crest cells to Schwann cells and then Hippo pathway in peripheral nerve injury and repair will also be illustrated.

Results:
Hippo pathway especially YAP/TAZ is essential in PNS development. The degree of YAP/TAZ's activation controls the NCC's fate.It has been substantiated that the BMP2-Smad2/4 signaling impedes NSC proliferation through antagonizing YAP-TEAD combinations and downregulating the expression of Cyclin D1[68]. This tallies with BMPs' role in NCCs. FAT1 cadherin, an upstream positive regulator of Hippo pathway, contributes to normal neuritogenesis and regulates Hippo pathway in neuronal differentiation of SH-SY5Y and NTera2 cell models.The delicate regulation of Hippo pathway is required for the proper repair of PNI.The Nrg1-ErbB4-YAP signaling was found in the MCF10A human breast cancer cell line to potentiate YAP-dependent cell migration

Conclusions:
To sum up, Hippo pathway is of great importance in PNS physiopathology, making good use of Hippo's regulation may be conducive to treatment and recovery of peripheral neuropathy.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Peripheral nervous system, Schwann cell, Schwann cell, Development, Damage repair

SARM1 deletion only provides marginal protection against axonal degeneration in CMT2J

Poster No:
P 042

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Introduction:
Charcot-Marie-Tooth disease type 1B (CMT1B) is a peripheral neuropathy caused by mutations in the myelin protein zero (MPZ) gene. MPZ encodes for P0, a key protein for peripheral myelin and therefore most MPZ mutations result in abnormal myelin formation. Markedly, the T124M (substitution of the threonine on position 124 by methionine) mutation causes a late-onset axonal neuropathy instead, referred to as CMT2J, that shows only minimal of myelination defects. A promising target that might be able to counteract this is SARM1 (sterile α and toll-like interleukin receptor motif-containing protein 1), known to be the central executioner of peripheral axonal degeneration.

Methods:
Therefore, we used the MPZ-T124M mouse model and crossbreed them with SARM1 knock-out mice. Electrophysiology, nerve morphology and their molecular properties have been assessed to determine the process and degree of axonal degeneration.

Results:
Unfortunately, SARM1 deletion did not significantly rescue the neuropathy of 12-month-old T124M mice. The nerve conduction velocity and compound motor action potential are lowered in homozygous T124M mice but remain unaltered in the double mutants. At earlier time points we could not observe a delayed disease onset or slowed progression either. However, in 12-month-old T124M mice lacking SARM1, there is a reduction in the concentration of plasmatic neurofilaments, a general biomarker for neurodegeneration. Additionally, through crossbreeding these mice with a Thy-YFP reporter line, we could observe reduced signs of degenerating axons like swollen tips and fragmentation.

Conclusions:
In conclusion, SARM1 deletion doesn't appear to be a suitable strategy to fully rescue axonal degeneration in CMT2J. It is not clear how a mutation in a myelin protein can induce axonal degeneration, but the pathomechanism is likely situated more upstream. Currently, we are investigating the effect of the T124M mutant P0 protein on the axo-glia exchange areas to characterise the glial mechanisms that support axonal survival.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Charcot-Marie-Tooth, MPZ, Axonal degeneration, SARM1

Clinical trial readiness for CMT: Establishing an online training and quality assurance program for Clinical Outcome Assessments

Poster No:
P 043

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Introduction:
Clinical trials in children and adults are underway for promising therapeutic candidates. For >10 years members of the Inherited Neuropathy Consortium (INC) have developed reliable, sensitive and responsive Clinical Outcome Assessments (COAs) for patients with CMT across the lifespan (CMTInfS, CMTPedS, CMT-FOM). This project seeks to continue to ensure rigor through development and implementation of a gold standard training and quality assurance program to maintain this excellent high standard and provide a framework for training new evaluators. The aims are to generate training resources though a collaborative process and to develop digitally enabled infrastructure for a clinical evaluator training and quality assurance program.

Methods:
eHealth training resources were co-designed with consumers (n=60) including CMT experts, clinical evaluators, pharmaceutical representatives, and patients through a collaborative, multi-method approach involving surveys and focus groups/interviews. Professional videos and still images of COA items were captured. The e-training and quality assurance platform was developed on www.ClinicalOutcomeMeasures.org and implemented across the INC.

Results:
International clinical evaluators identified availability of training resources as a barrier to reliable/precise COA use. Video demonstrations, online workshops and labeled videos and photographs were ranked as the top 3 training methods. The training and quality assurance program was developed and includes interactive high-quality videos, featuring patients with a range of disease severity, of all items with examples of correct/incorrect techniques, expert tutorials on outcome assessment theory, online quizzes with feedback and certification and reliability assessments for observational items. 40 clinical evaluators from the INC have been trained and are reliable using this training and quality assurance program.

Conclusions:
The digitally enabled clinical evaluator training and quality assurance program addresses the training needs of CMT clinical evaluators. Inaccurate measurement causes unnecessary delays in the translation of new therapies. This gold standard training program ensures high quality, reliable data is collected by trained clinical evaluators.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: Muscular Dystrophy Association Ideas Grant (https://doi.org/10.55762/pc.gr.147562) Inherited Neuropathy Consortium Pilot Grant

Keywords: Charcot-Marie-Tooth disease, Clinical Trials, Clinical Outcome Assessments, Online Training, Reliability

Morphological study of Pacinian corpuscles across different mammalian species

Poster No:
P 044

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Introduction:
Pallesthesia defines our ability to feel vibrations. We can feel this sensation when we explore a surface with our fingertip or touch a moving object. Pacinian corpuscles (PCs) are skin mechanoreceptors involved in high frequency vibration perception. In a previous study, we have shown that human PCs are most sensitive to 250 Hz, while mice are more sensitive to frequencies around 1000 Hz. To test whether the tuning differences between species were related to structural differences, we conducted a comparative study of the shape, distribution and innervation of the PCs in the forelimbs of 3 mammalian species: mouse, a small prosimian primate (mouse lemur) and human.

Methods:
For this translational study, we implemented, for each sample from these mammals, histological techniques, such as immunohistochemistry coupled with tissue-clearing, light-sheet microscopy, ultra-expansion microscopy, standard histology and electron microscopy.

Results:
We demonstrated that all three species have high concentration of PCs along the bones of their forelimbs, which are innervated by the anterior interosseous nerve. Unlike in the two primates, PCs are absent in the glabrous skin of the paws in mice. There is a significant difference between the species in the overall size, shape and organization of the PCs. Whereas in humans, PC diameters are on average ~569 μm, lemurs and mice have much smaller PCs (~83 μm and ~58 μm). In addition to cross-species variation in size, we also noted size differences within species. In mice, PCs of digits are smaller than those found along the forearm. As for the two primates, they show a wide diversity of shapes and sizes of Pacinians along the forelimb.

Conclusions:
Our analysis revealed substantial differences in size and organization of PCs across different mammals. As next steps we want to correlate the differences in morphology to the frequency tuning observed, by conducting electrophysiological recordings in individual PCs.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: vibrations, mechanoreceptors, cross-species, tissue-clearing, microscopy

Natural history study of SORD neuropathy

Poster No:
P 045

Authors:
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Introduction:
We have recently established biallelic mutations in the sorbitol dehydrogenase (SORD) gene as a common and potentially treatable cause of axonal neuropathy. This global observational study aims at reporting the full genotype-phenotype spectrum of SORD neuropathy and at defining valid outcome parameters for future clinical trials.

Methods:
Through an international network of collaborators, we have identified 144 individuals with biallelic mutations in SORD. Clinical data were collected according to a standardized protocol.

Results:

113 cases carried the common c.753delG;(p.Ala253GlnfsTer27) variant in a homozygous state. In 25 cases, the c.753delG variant was found in compound-heterozygosity with a second missense or nonsense variant, including c.458C>A;(p.Ala153Asp) (n=20), while 6 cases had different sequence variants on the two alleles. Fasting serum sorbitol level was measured and elevated in 31 cases (14.7±4.9 gr/L, n.v.<0.25), without significant differences across different genotypes. Patients were diagnosed with CMT2 (59%), dHMN (37), and CMT intermediate (4%). The mean age of symptom onset, including difficulty walking and running, was 17.7±9.2 years (range 3-50 years). Foot dorsal and plantar flexion were weak (MRC<5) in 95% and 79% of patients, respectively, while sensation was preserved in over 60% of the cases. 40% of patients required ankle foot orthosis and 13 needed a stick. MRC scores of foot dorsiflexion correlated inversely with the age of the subjects and declined significantly over 1 year.

Conclusions:
SORD neuropathy appears to be a frequent recessive form of axonal, motor predominant CMT, with prominent foot dorsal and plantar flexion involvement. Fasting serum sorbitol is a reliable biomarker of the condition and can provide functional validation of variants within the expanding genotype spectrum of the disease. Foot dorsiflexion strength represents a promising outcome measure which should be considered in therapeutic trials on this condition.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: CMT, SORD

An induced pluripotent stem cell-based model to study neurodegeneration in RFC1 disease.

Poster No:
P 046

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Introduction:
Cerebellar ataxia, neuropathy and vestibular areflexia syndrome (CANVAS) is a late-onset, slowly progressive ataxia associated with biallelic AAGGG expansions in RFC1. The phenotypic spectrum of RFC1 disease is broad but sensory neurons are constantly involved. The disease mechanisms of this disorder remain elusive and previous studies on patients' cell lines (i.e., fibroblasts, lymphoblasts) or post-mortem brains did not show a reduction of RFC1 RNA or protein. Recently, induced pluripotent stem cells (iPSCs) have been proposed as a powerful experimental model for several diseases, as they allow to generate patient-specific cell lines from different sources. We generated IPSC-derived sensory neurons to investigate the disease mechanisms of RFC1 disease.

Methods:
We used Chamber's modified protocol for the differentiation of sensory neurons starting from IPSC lines derived from patients' and controls' fibroblasts. We assessed morphological parameters such as neurite outgrowth and number of branching points. We then compared the transcriptome profile of CANVAS and control lines by RNAseq (Illumina Next Seq 500). Finally, given the role of RFC1 in DNA damage, we quantified DNA damage response in basal conditions and after pharmacological stress, as well as axonal damage markers (neurofilament light chain).

Results:
We successfully generated mature and pure colonies of post-mitotic sensory neurons derived from IPSCs lines (n=3 CANVAS; n=3 controls). No significant difference in neurite outgrowth and branching points was observed between patients and controls. The transcriptomic analysis on three CANVAS vs three control lines revealed unchanged RFC1 transcription and splicing. Quantification of RFC1 protein, DNA and axonal damage markers is still ongoing.

Conclusions:
The study confirmed no overt reduction of RFC1 transcript or abnormal splicing in a disease relevant model as IPSC-sensory neurons. Future studies on long-term cultures of IPSC-derived neurons will provide a better insight into the mechanisms and pathways underlying neurodegeneration in this disorder.

References:
No

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References 4:

Grant Support:

Keywords: CANVAS, IPSC, Axonal degeneration

Aminolevulinic Acid Dehydratase Porphyria: A Ultrarare and Treatable Early-Onset Axonal Neuropathy

Poster No:
P 047

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Introduction:
Aminolevulinic Acid Dehydratase (ALAD) porphyria is an ultrarare recessive disorder with only 8 reported cases in the world literature and caused by a deficiency of ALAD enzyme that catalyses the second step in heme biosynthesis.

Methods:
We report clinical, neurophysiological and genetic findings in two siblings, 7 and 14 years old, born from consanguineous Moroccan parents.

Results:
Their older sister, had a history of severe intellectual disability, axonal neuropathy, hypertension and cyclic vomiting, and died at 10 years for renal and respiratory failures. The 2 siblings presented with congenital severe hypotonia due to axonal polyneuropathy and developmental delay. A moderate ID in the younger girl and a profound sensorineural hearing loss in both were identified. From the age of 5 and 12 years respectively they presented with recurrent episodes of severe abdominal pain, nausea and vomiting, subsequently associated with intense neuropathic pain and progressive weakness requiring wheelchair use and respiratory support. Neurophysiologic studies detected severe worsening of neuropathic changes. In addition, during those episodes they presented hypertensive crises requiring intensive care. The older brother also experienced behavioural changes, hallucination and severe sleep problems. Clinical and neurophysiological data gradually ameliorated after the neurovisceral crisis. Whole exome sequencing analysis identified a homozygous ALAD variant together with a PEPT2 polymorphism reported to affect the severity and prognosis of porphyria-associated kidney disease. Measurement of urine porphyrins ensured the diagnosis. RNAi therapy with givosiran was started with significant reduction of attack rates. Interestingly, homozygous PCDH15 variants were also detected, possibly responsible for the sensorineural hearing loss.

Conclusions:
The diagnosis of acute porphyria attack is challenging due to the variable clinical presentation and similarities with other neurological conditions; an early diagnosis, timely intervention, and the avoidance of precipitating factors are crucial as untreated acute attacks can progress and potentially lead to permanent neurological damage, or even be life-threatening.

References:
No

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Grant Support:

Keywords: Porphyric neuropathy, Porphyria, ALAD, gene therapy

ACTIVATION OF THE IRE1/XBP1 BRANCH OF THE UPR AMELIORATES DISEASE PARAMETERS IN PROTEOTOXIC NEUROPATHIES

Poster No:
P 048

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Introduction:
Myelin protein zero (P0), encoded by the MPZ gene, is the most abundant protein in myelin of peripheral nerves. In humans and mice, MPZS63del and MPZR98C mutations cause mild and severe Charcot-Marie-Tooth (CMT) type 1B, respectively. Both P0S63del and P0R98C mutant proteins are retained in the endoplasmic reticulum (ER) where they activate an unfolded protein response (UPR). The UPR is characterized by the activation of the PERK/eIF2alpha, ATF6 and IRE1/Xbp1 pathways. We have previously reported that the genetic and pharmacologic modulation of PERK/eIF2alpha is protective in CMT1B, but the role of the other UPR branches remained largely unknown. IRE1, through its RNAse domain, leads to the unconventional splicing of Xbp1, generating Xbp1s, a potent transcription factor that activates genes involved in protein folding and degradation

Methods:
To investigate the IRE1 pathway in CMT1B, we generated new models of CMT1B in which Xbp1s is deleted or overexpressed in Schwann cells specifically. Moreover, we explored compounds that selectively activate IRE1 induced Xbp1 splicing in myelinating dorsal root ganglia (DRGs).

Results:
We observed that the absence of Xbp1 dramatically worsened dysmyelination as well as electrophysiological and locomotor parameters in young and adult MpzS63del and MpzR98C mice. This suggests that the activation of Xbp1s targets, that RNAseq analysis identified as mostly ER-associated degradation genes, plays a critical role in limiting mutant P0 toxicity, which cannot be compensated by other stress responses. Remarkably, in both MpzS63del and MpzR98C mice overexpressing Xbp1s, we observed an improvement of disease parameters, such as myelin thickness and nerve conduction velocities. Accordingly, compounds activating Xbp1s improved myelination in MpzS63del DRG cultures.

Conclusions:
Altogether, these data demonstrate that the IRE1/Xbp1 pathway has a critical adaptive role in proteotoxic neuropathies and suggest that its pharmacologic activation may represent a therapeutic option for CMT1B and for other neuropathies characterized by UPR activation.

References:
No

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References 4:

Grant Support:

Keywords: Schwann cell, myelin, CMT neuropathy, Unfolded Protein Response, ER-stress

SPTAN1 is associated with a spectrum of intellectual disability and axonopathy

Poster No:
P 049

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Introduction:
SPTAN1, encoding alpha-II-spectrin, displays an astonishing phenotypical heterogeneity ranging from developmental and epileptic encephalopathies (DEE), hereditary motor neuropathy (HMN), hereditary spastic paraplegia (HSP) and spinocerebellar ataxia (SCA). Our research group hypothesized destabilization of spectrin repeats for the HSP and SCA cohort, and haploinsufficiency through nonsense-mediated mRNA decay for the HMN cohort. However, full understanding of the genotype-phenotype correlations in these so-called neurospectrinopathies is incomplete.

Methods:
Review of currently reported SPTAN1 variants and their associated phenotypes. Inclusion of genetic and clinical details of additional families referred to our center with recurrent or novel SPTAN1 mutations identified through whole exome sequencing.

Results:
In total 61 different SPTAN1 mutations in 108 patients are reported to date. Herein the highly recurrent (19 patients) p.Arg19Trp mutation is associated with HSP and nonsense mutations with HMN (13 patients) or intellectual disability (ID) (6 patients). Eight additional families were referred to our center. Three families carry the p.Arg19Trp mutation of which 2 show a pure HMN and one patient pure HSP phenotype. Four families carry novel nonsense mutations (p.Arg801*, p.Glu655*, p.Asp1676* and p.Gln2247*) and show variable involvement of the central (HSP) or peripheral (HMN) axons with moderate ID and thin corpus callosum in one patient. Finally, one patient developed a childhood-onset distal weakness suggestive for HMN and carried a de novo splice-site mutation (c.4906-1G>A).

Conclusions:
We add eight additional families carrying SPTAN1 variants and expand both the p.Arg19Trp and the haploinsufficiency spectrum towards complex forms of central or peripheral axonopathy and ID. Intriguingly biallelic variants leading to predicted loss of function in SPTBN4, encoding beta-III-spectrin which together with alpha-II-spectrin forms the backbone of the axonal membrane periodic system, is equally associated with the ID and axonopathy spectrum. Further research is needed to study the underlying and possibly shared pathomechanisms.

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No

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Grant Support:

Keywords: SPTAN1, Axonopathy, Intellectual disability

Electrophysiological features of the peripheral neuropathy in cerebellar ataxia, neuropathy, vestibular areflexia syndrome (CANVAS)

Poster No:
P 050

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Introduction:
Our aim was to describe the electrophysiological features of the peripheral neuropathy encountered in CANVAS.

Methods:
Were included 32 patients (19 females) with a median age of 71 years, with a pathological homozygous expansion of the (AAGGG)n type in intron 2 of the RFC1 gene. Electrophysiological investigations comprised: motor conduction study (median, ulnar, tibial, fibular nerves), sensory conduction study (sural, median, ulnar, radial, medial and lateral cutaneous nerve of the forearm), H-reflexes in median and tibial nerves, blink reflex, electrochemical skin conductance measured by Sudoscan, sympathetic skin response, heart rate variability on deep breathing and needle examination.

Results:
Distal motor amplitudes were normal in 23/32 cases. Distal sensory amplitudes were decreased in the upper and lower limbs in 30 cases and only in the lower limbs in 2 cases. Sensory and motor conduction velocities were normal. H-reflexes were impaired in 11/12 median nerves and 17/18 tibial nerves. H-reflexes were abnormal in 4/5 patients with preserved Achilles reflexes. Blink reflex was abnormal in 5/17 cases (29%): R1 latency and R2 latency in respectively 2 and 3 cases. Sudoscan was abnormal in 10/26 cases (38%). Sympathetic skin response was abnormal in 3/9 cases (33%). Heart rate variability on deep breathing was abnormal in 4/15 cases (27%). Chronic denervation on needle examination were recorded in 7 patients (24%) in the anterior tibial muscle.

Conclusions:
Most of the patients (25/32, 78%) had a sensory neuronopathy, even when tendon reflexes were preserved. Involvement of sensory neurons of small caliber fibers or of the brainstem (V1 territory) is scarcer, found respectively in 36 and 29% of cases. CANVAS preferentially affects the peripheral sensory neurons of the large calibre fibres innervating the skin and the muscle spindles of the gamma fibres.

References:
No

References 1:

References 2:

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Grant Support:

Keywords: CANVAS, electrophysiology, neuronopathy

Human Dental Pulp Stem Cells as a Patient-in-a-dish Model for Charcot-Marie-Tooth Disease Type 1A

Poster No:
P 051

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Introduction:
Charcot-Marie-Tooth disease type 1A (CMT1A) is the most prevalent demyelinating peripheral neuropathy worldwide. The disease is caused by a peripheral myelin protein 22 (PMP22) gene duplication, which is predominantly expressed by Schwann cells. CMT1A drug development is limited by the absence of clinically relevant disease models. Remarkably, human Dental Pulp Stem Cells (hDPSC) are a subset of mesenchymal stem cells and share their embryonic origin with Schwann cells: the neural crest. Our research group has pioneered the differentiation of hDPSC towards functional myelinating Schwann cells. We aim to establish a novel human in vitro model for CMT1A based on hDPSC-derived Schwann cells (hDPSC-SC).

Methods:
hDPSC were isolated from the dental pulp of healthy donor third molars using the explant method. Six donor hDPSC were differentiated into hDPSC-SC to validate the consistency of the protocol by qPCR and immunocytochemistry. Next, PMP22 overexpression was induced in hDPSC and hDPSC-SC by lentiviral transduction and CRISPR-Cas9 to mimic CMT1A. qPCR and PCR were performed to confirm elevated PMP22 expression.

Results:
Following differentiation, six donor lines expressed relatively stable mRNA and protein levels of Schwann cell markers (P75, S100B, SOX10, laminin211, and laminin 411). Relative mRNA expression of myelin markers (MBP, NCAM, C-JUN, and KROX20) was consistent in three differentiated hDPSC-SC lines. Moreover, PMP22 mRNA levels were upregulated in hDPSC and hDPSC-SC after lentiviral transduction. Additionally, PCR confirmed the successful integration of one additional PMP22 copy in hDPSC using CRISPR-Cas9.

Conclusions:
Consistent Schwann cell differentiation was confirmed by stable expression levels of Schwann cell and myelination markers. Additionally, we have successfully overexpressed PMP22 in hDPSC-SC and hDPSC using lentiviral transduction and CRISPR-Cas9, respectively. Following optimization, these PMP22-overexpressing hDPSC-SC will serve as a novel human model for CMT1A. Due to its high clinical relevance, this model provides opportunities for translatable CMT1A research and drug screening.

References:
No

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References 2:

References 3:

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Grant Support: This project is funded by the Charcot-Marie-Tooth Association (CMTA) and Fonds Wetenschappelijk Onderzoek (FWO) Flanders.

Keywords: Charcot-Marie-Tooth disease type 1A, Schwann cells, Human Dental Pulp Stem Cells, Peripheral Myelin Protein 22, In vitro models

Charcot-Marie-Tooth Subtype Biomarkers and Outcome Measures in Subjects with CMT1B, CMT2A, CMT2F and CMT1X

Poster No:
P 052

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Introduction:
Natural history studies of CMT1B, CMT2A, CMT1X and CMT2F (the four genes) utilizing the CMT Neuropathy Exam Scores (CMTNS/CMTES), recent clinical outcome assessments (COA) such as CMT Functional Outcome Measure (CMT-FOM) and CMT Health Index (CMT-HI) are being collected at five international sites. These measures are being collected in combination with magnetic resonance imaging (MRI of calf and thigh), plasma and skin biopsy sample. The data collected (mentioned above) can be used to learn about the four disorders, to help develop therapies and to achieve 'clinical trial readiness' over time periods that are reasonable for industry partners.

Methods:
The objective is to prospectively measure the natural history of patients with CMT1B, CMT2A, CMT1X and CMT2F correlating subject's clinical outcome assessments, MRI imaging and plasma and skin samples over a 12-month period. Each subject will complete two visits baseline and a 12-month follow-up visit. Clinical information from each visit is electronically submitted and maintained in a database housed at the Rare Disease Clinical Research Network (RDCRN) at the Data Management and Coordinating Center at Cincinnati Children's Hospital.

Results:
Overall, 140 patients have been enrolled across the study's five participating sites. This can be broken down into 32 CMT2A, 67 CMT1B, 41 CMT1X. Enrollment for CMT2F has just begun. Across the study sites, 140 baseline and 58 follow-up visits have been completed.

Conclusions:
Study recruitment for all sites is ongoing and will continue to facilitate clinical trial readiness for CMT1B, CMT2A, and CMT1X and CMT2F. With 140 subjects currently enrolled, all sites continue to work towards the goal of 60 subjects in total (15 subjects per gene).

References:
No

References 1:

References 2:

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Grant Support: Funding for this research is provided by the CMTA.

Keywords: CMT, Charcot-Marie-Tooth, Neuropathy

Plasma and Skin Biomarkers for Charcot-Marie Tooth Disease

Poster No:
P 053

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Introduction:
While several candidate biomarkers that have been developed for CMT1A, it is important to establish if similar biomarkers apply to other common forms of Charcot Marie Tooth (CMT) disease, including CMT1B, CMT1X, and CMT2A. Since pilot studies showed elevated levels of microRNA's in plasma from CMT1X, 1B and 2A, the goal of this study was to determine if microRNA's (miR) are elevated in larger cohorts of CMT, and to determine if Schwann cell-derived transcripts in skin can serve as biomarkers of other types of CMT. The larger cohorts enable better correlations with other outcome measures.

Methods:
We have collected plasma and skin samples from individuals with genetically confirmed cases of CMT1B, CMT1X, and CMT2A, and are evaluating plasma samples using microRNA profiling. We also have screened for Schwann cell-enriched transcripts using Nanostring analysis of skin biopsies with a custom gene Codeset based on bioinformatic analysis of peripheral nerve data sets from CMT1B mouse models. Biomarker levels are correlated with other patient data to test if biomarkers levels correlate with disease severity.

Results:
Initial screening of plasma miRNA from pilot cohorts revealed that muscle-derived microRNA's (myomirs) are elevated in CMT1B, 1X, and 2A compared to controls. The myomiRs likely reflect the progressive muscular atrophy. In addition, we have further developed a Nanostring transcript detection assay to apply to larger cohorts of CMT1B and CMT1X, and several candidate biomarkers have emerged from pilot studies of these forms of CMT.

Conclusions:
Biomarkers for CMT may be subtype-specific based on the unique pathogenesis of each CMT subtype, but others may reflect common processes involved in CMT progression, and our data sets allow comparative analysis across major CMT subtypes. The elevation of muscle-derived myomiR's likely reflects ongoing muscular atrophy in individuals with CMT, and it is possible that this could provide a complementary biomarker in clinical trial design for CMT.

References:
No

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Grant Support: Charcot-Marie-Tooth Association

Keywords: CMT, Charcot-Marie-Tooth, Neuropathy, Biomarkers

Novel Gain-of-function Variant Dysregulates Sphingolipid Production and Links SPTLC2 with Juvenile-onset Amyotrophic Lateral Sclerosis

Poster No:
P 054

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Introduction:
Amyotrophic lateral sclerosis (ALS) is a progressive motor neuron disease leading to paralysis and death. The enzyme complex serine-palmitoyltransferase (SPT) conjugates L-serine and palmitoyl-CoA to form sphingoid bases - the first and rate-limiting step of sphingolipid (SL) de-novo synthesis. Recently, ALS patients were identified with specific pathogenic mutations in the SPTLC1 subunit, rendering SPT irresponsive to its regulatory subunit ORMDL3, which leads to excessive sphingolipid formation.

Methods:
We screened the GENESIS database containing 700 motor neuron disease cases to search for gain-of-function pathogenic variants in SPTLC2, encoding the second catalytic subunit of the SPT complex. Mutations were confirmed and co-segregation studies performed by Sanger sequencing. Using high resolution mass spectrometry, the sphingolipid profile was analyzed in patient plasma and HEK cells transfected with mutant SPTLC2.

Results:
Presenting with progressive proximal and distal muscle weakness, oral fasciculations, and pyramidal signs, we identified two unrelated patients with juvenile-onset ALS, both carrying the de-novo variant p.Met68Arg in SPTLC2. This variant affects a highly conserved amino acid position within a single short transmembrane domain of SPTLC2. While methionine is a hydrophobic residue, arginine has an additional guanidine group that is protonated at neutral pH, suggesting that p.Met68Arg interferes with ORMDL3 interaction. Indeed, both patients' plasma sphingolipid profiles showed a significant increase in ceramides and complex SLs. Accordingly, excessive sphingolipid overproduction was confirmed in mutant-expressing HEK cells.

Conclusions:

Specific gain-of-function variants in both SPT core subunits affect the homeostatic control of SPT. The SPTLC2 p.Met68Arg variant occurred de-novo in two independent children, who presented with a clinical phenotype and sphingolipid profile that were both highly consistent with ALS-causing SPTLC1 mutations. We conclude that SPTLC2 is a new Mendelian ALS gene. Given the direct interaction of SPTLC1 and SPTLC2, targeting this pathomechanism might open therapeutic opportunities for ALS.

References:
No

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References 2:

References 3:

References 4:

Grant Support: NIH, German Research Foundation

Keywords: Amyotrophic lateral sclerosis, Sphingolipid metabolism, Gene discovery, Genotype-phenotype correlations, Hereditary Sensory and Autonomic Neuropathy

Impact of fat and lean mass on disability in children with Charcot-Marie-Tooth disease

Poster No:
P 055

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Introduction:
Neuromuscular diseases cause alterations in body composition due to changes in relative proportions of fat-free mass and fat mass, potentially impacting disability. Children with CMT who are severely underweight or obese, by Body Mass Index (BMI), are more disabled as measured on the CMT Pediatric Scale (CMTPedS), than those of a healthy weight. A change in BMI away from a healthy range is also associated with increasing disability. However, BMI cannot differentiate between fat-free mass and fat mass. The aim of this study was to explore the association between body composition and disease severity in children with CMT.

Methods:
Children with CMT (4-18 years) were recruited for this study. Fat mass index (FMI), fat-free mass index (FFMI) and lean mass z-scores were evaluated with bioelectrical impedance analysis (BIA, Tanita MC-780MA) and disease severity was assessed using the CMTPedS during a single study visit.

Results:
Eighty-one children were assessed (58% male) of whom 3.7% were severely underweight; 13.6% underweight; 56.8% healthy weight;16.0% overweight and 9.9% obese. Both FMI and FFMI strongly correlated with BMI (rho= 0.896 $p<0.001$ and rho = 0.853 $p<0.001$ respectively). There was a moderate correlation between FMI (a marker of adiposity) and the CMTPedS scores (rho = 0.494, $p<0.001$) and moderate inverse correlation between lean mass z-score and CMTPedS scores (rho = -0.313, $p=0.04$).

Conclusions:
A higher fat mass and lower lean mass is associated with greater disability in children with CMT. Targeted interventions should focus on building muscle mass and keeping fat mass within healthy range with exercise and nutritional advice based on underlying BIA abnormality.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Charcot-Marie-Tooth Disease, Body Composition, Outcome measure, BMI, Pediatrics

The Effect Of Orthoses And Vibration On Balance In Charcot-Marie-Tooth disease: A Proof-Of-Concept Study

Poster No:
P 056

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Introduction:
People with Charcot-Marie-Tooth disease and related disorders (CMT) frequently report problems with balance. Adaptations to improve foot posture and aid stability are prescribed, though few studies have looked at whether they affect balance. Vibration to the foot has shown promise in improving balance in older people, diabetic neuropathy and when applied to proximal muscle groups in CMT. So far application to the sole of the foot has not been explored in CMT. Objectives To investigate the effect of two interventions on postural stability in people with CMT: (1) external ankle support; (2) vibratory stimulation to the sole of the foot.

Methods:
A cross-sectional design was used in this proof-of-concept study. External support was provided by a Push Aequi Ankle Foot Orthoses (AFO) worn with footwear, and vibration was delivered via an insole with three vibrating elements. Laboratory based posturography measures were used to assess postural stability in the three conditions (AFO, Vibration and No Vibration).

Results:
13 participants were recruited (n=6 with demyelinating IPN and n=5 with Axonal disease). The AFO condition demonstrated moderate improvements in balance with reduced body sway (Hedges' g=0.53). The vibratory input caused a small decrease in balance ability, with increases in body sway (Hedges' g=0.22).

Conclusions:
The Push Aequi AFO may provide a mechanical stiffening to stabilise the ankle plus sensory feedback from cutaneous receptors. A decline in balance performance with vibratory input to the sole of the foot in this group contrasts previous work in diabetes. The vibratory input may act as noise to an already compromised sensory system. Previous work has shown improvements in balance in people with CMT1A following perturbation training. Vibratory insoles are worth considering as a perturbation method in this type of intervention.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Charcot-Marie-Tooth, Physiotherapy, Rehabilitation, Balance, Falls

Amyloid Deposition in Wild-type and Familial Transthyretin Amyloid Polyneuropathy at the Distal Limb

Poster No:
P 057

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Introduction:
We assessed the sensitivity of transthyretin amyloid detection using Congo red and immunohistochemistry against misfolded-TTR among ATTRv, ATTR-CM (cardiomyopathy) as well as in patients who presented with peripheral neuropathy (PN).

Methods:
Six groups of subjects were studied: (1) ATTRv with PN (ATTRv-PN, n=26), (2) asymptomatic ATTRv carriers but have no PN (ATTRv-noPN; n=11), (3) patients who presented with PN, possessed no pathogenic TTR mutations (ATTRwt-PN, n=6), (4) patients with ATTRwt-CM (n=19) (5) healthy controls (n=18) and (6) diabetic neuropathy disease controls (n=40). Patients underwent examination (NIS), electrophysiology and 3mm skin biopsies. 50µM skin sections were assessed for intraepidermal nerve fiber density (IENFD), sweat gland nerves and TTR amyloid by anti-misfolded TTR immunohistochemistry and Congo red. All data were expressed as the mean + SD.

Results:
Amyloid was detected in 100% of ATTRv-PN subjects in least at one leg site. The diagnostic sensitivity and specificity to detect amyloid with Congo red and IHC in subjects with ATTRv-PN were 92% and 100%. ATTRv-PN cases had a higher and more variable cutaneous amyloid burden (14.62+24.2%) compared to ATTRv-noPN cases (6.0+12.1%), ATTRwt-PN: 2.3%, ATTRwt-CM: 3.5% and none in controls. Intraepidermal and sweat gland nerves degenerated across the spectrum of ATTR disease. In ATTRv-PN, IENFD reduction correlated with NIS-LL ($p<0.0001$, $r=-0.63$) sural ($p=<0.05$, $r=0.58$) and peroneal nerve ($p<0.05$, $r=0.51$) amplitudes indicating high amyloid burden impair nerve functions. In ATTRwt-PN, the NIS-LL score increased (34.7+29.1) and in ATTRwt-CM, IENF degeneration was associated with NIS-LL score ($p=<0.0001$, $r=-0.65$) at the distal leg.

Conclusions:
Evaluation of skin punches can be an important diagnostic tool in ATTRv and ATTRwt cases. Immunohistochemistry against anti-misfolded TTR is more sensitive than Congo red in detecting amyloid. The pattern of amyloid deposition in ATTRv is distinct from ATTRwt.

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Yes

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References 4:
Lam L, Margeta M, Layzer R. Amyloid polyneuropathy caused by wild-type transthyretin. Muscle & nerve. 2015;52:146-9

Grant Support:

Keywords: ATTRwt, ATTRv, Transthyretin, Congo red, Epidermal nerves

Digital Outcome Measures of Gait and Balance in Adults with Charcot-Marie-Tooth Type 1A

Poster No:
P 058

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Introduction:
There is much activity in the pre-clinical space for Charcot-Marie-Tooth neuropathy and therefore, clinical trial preparedness is essential. Advances in technology have fostered the use of digital outcome measures in clinical trials. Specifically, wearable sensors have been developed to provide discrete measures of gait and balance. These outcome measures may be more sensitive than disease-specific functional outcome measures or traditional timed tests used to assess individuals with Charcot-Marie-Tooth (CMT) and therefore, may supplement these outcome measures in future clinical trials.

Methods:
As part of an ongoing, international, natural history study, 100 adults with CMT1A are being recruited to examine the reliability, validity and sensitivity of gait and balance metrics derived from wearable sensors. Participants wear sensors with tri-axial accelerometers at their waist and around their feet while performing gait and balance assessments at serial, 6-month visits. Participants also complete a standardized clinical outcome assessment, the CMT-Functional Outcome Measure (CMT-FOM), during their in-person visit.

Results:
Adults with CMT1A have completed baseline assessments of gait and balance the wearing sensors. Individuals with CMT1A have increased step duration, decreased gait speed and decreased stride length compared to normative data. Derived metrics of gait and balance (sway area, jerk, path length) are moderately correlated with the total CMT-FOM score. These metrics, with the exception of sway area, are significantly different between those above and below the mean CMT-FOM score.

Conclusions:
Individuals with CMT1A demonstrate altered gait and balance function as compared to normative data. Cross-sectional metrics of gait and balance are correlated with measures of strength and function. Data from this study will help evaluate the utility of gait and balance digital outcome measures for future clinical trials.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: U54 NS0657

Keywords: digital biomarkers, CMT, Outcome measures, wearable sensors, gait

NanoCur for CMT1A: Preclinical Investigation of a Next Generation Therapy

Poster No:
P 059

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Introduction:
CMT1A is the most prevalent form of Charcot-Marie-Tooth disease commonly associated with a duplication of the PMP22 gene, which leads to peripheral demyelination and ultimate sensorimotor loss. While therapies are lacking, we sought to investigate the therapeutic properties of curcumin, which was previously shown to exert beneficial effects on peripheral nerve function in several types of neuropathies. Despite the wide range of biological activities associated with it, including antioxidation and anti-inflammation, this compound presents with unfavorable pharmacokinetics. For this purpose, we have developed curcumin loaded cyclodextrin/cellulose nanocrystals (NanoCur) to bypass this limitation.

Methods:
This study aims to assess the effect of NanoCur treatment in CMT1A rodent models and compare its efficacy to Theracurmin®, a commercially available curcumin formulation, while elaborating on the in-vivo toxicity and mechanism of action of the compound. For that, daily injections of low doses of NanoCur were administered intraperitoneally for rats and mice for 12 weeks and 8 weeks, respectively. Neuropathy was assessed through motor nerve conduction velocity (MNCV), Catwalk gait analysis, Beam Balance, Grip strength and Rotarod. Biochemical and histological analyses of myelin phenotype and markers of inflammation were also performed on the sciatic nerves of the different experimental groups.

Results:
Our results show an improved motor function in the NanoCur-treated CMT1A rodents, associated with an improvement in the myelin phenotype within the nerve. To our interest, these effects are not significant upon treatment with a similar dose of Theracurmin. Furthermore, NanoCur treatment appears to perform its effect through an alleviation of inflammatory pathways, involving macrophage recruitment to the diseased nerve. That was combined with the absence of any systemic toxicity.

Conclusions:
Therefore, NanoCur significantly associates with therapeutic benefits at the cellular and functional levels in CMT1A with minimal systemic toxicity, promoting it as a potential therapeutic candidate for CMT1A disease and, possibly, other forms of neuropathies.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: AFM-Telethon

Keywords: CMT1A, preclinical , NanoCur, Therapy, Neuropathy

Late Onset Axonal Peripheral Neuropathy Potentially Caused by Spinocerebellar Ataxia 8 expansion

Poster No:
P 060

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Introduction:
Hereditary spinocerebellar ataxia 8 (SCA8) is caused by CTG-CAG repeat expansions in the ATXN8OS/ATXN8 genes. Pathogenic alleles contain 71 to >1,300 repeats. Classic symptoms include spasticity, dysarthria, gait instability, and eye movement abnormalities. Sensory neuropathy, cognitive impairment, parkinsonism, and progressive supranuclear palsy (PSP) have also been reported. We identified two unrelated patients with axonal peripheral neuropathy who have SCA8 expansions.

Methods:
Patient evaluation included neurological exam and nerve conduction velocities. Phenotype-driven genetic testing was performed with reflex to long read whole genome sequencing (WGS) on a clinical basis. Data was reviewed through the Genesis platform.

Results:
UIA-102903-0001: 72yo man with balance difficulty, left leg weakness, and loss of touch sensation in lower extremities (LE). He had bilateral pes cavus and tight Achilles tendons. Exam showed length dependent sensorimotor peripheral neuropathy. LE reflexes were absent. He had a wide-based, unsteady gait. No evidence of cerebellar involvement. Nerve conduction velocities (NCVs) showed axonal neuropathy. His CMTNS was 6/36 (mild range). Inherited neuropathy panel was negative; WGS showed an 82-repeat expansion, orthogonally confirmed by an outside laboratory. UIA-102945-0001: 65yo man with decreased balance and loss of touch sensitivity in LE. He had bilateral pes cavus and calf atrophy. Exam showed a length dependent sensorimotor neuropathy. Reflexes were absent at knees and normal at ankles. He had a wide based gait. No evidence of cerebellar involvement. NCVs showed axonal neuropathy. CMTNS was 10/36 (mild range). Neuropathy panel was negative; WGS showed a 92-repeat expansion, orthogonally confirmed by an outside laboratory.

Conclusions:
Presented are two unrelated patients with late onset, axonal peripheral neuropathy with an associated short SCA8 repeat expansion. These patients with similar presentations indicate that SCA8 may cause an axonal peripheral neuropathy without ataxia. More data will be required to determine if these are more than associations and could expand the SCA8 phenotype.

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Yes

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References 4:

Grant Support: Inherited Neuropathy Consortium (INC)

Keywords: CMT, axonal, SCA8, phenotype, ATXN8OS/ATXN8

Development of a Disability Scale for Riboflavin Transporter Deficiency

Poster No:
P 061

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Introduction:
Riboflavin Transporter Deficiency (RTD) is a rare neurodegenerative disorder of childhood onset characterised by pontobulbar palsy, ataxia, limb muscle weakness, and sensorineural deafness. Accurate assessment of functional change, with a RTD-specific outcome measure, is essential to quantify the benefit from riboflavin supplementation and evaluate the effectiveness of additional disease modifying therapies.

Methods:
Previous assessments of individuals with RTD using the Charcot-Marie-Tooth disease Pediatric Scale (CMTPedS) were reviewed, and individual scale items were evaluated for their appropriateness in assessing RTD-specific deficits. A literature search was performed for existing clinical outcome assessments that measure outcomes specific to RTD not evaluated by the CMTPedS, such as proximal weakness. The new scale was trialled over two years in five patients.

Results:
Balance impairments, sensory loss and proximal weakness are primary symptoms of individuals with RTD. These impairments were the focus of changes made to the CMTPedS when modifying for individuals with RTD. For the RTDPedS, items with floor and ceiling effects were removed and two additional items (Elbow Flexion and the 30 Second Sit-to-Stand test) were added to the scale from the 1000 Norms Project to assess proximal strength and function. Assessment of the 5 patients with RTD, treated with Riboflavin, using the RTDPedS showed good sensitivity over 2 years to disease specific impairments and progression, no ceiling or floor effects, and good inter-rater reliability despite the small sample size.

Conclusions:
The newly-developed RTDPedS will provide accurate and reliable assessment of impairment for individuals with RTD. This will ensure clinical trial readiness for potential future therapies to treat RTD.

References:
Yes

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McKay MJ, Baldwin JN, Ferreira P, et al. Reference values for developing responsive functional outcome measures across the lifespan. Neurology. Apr 18 2017;88(16):1512-1519. doi:10.1212/WNL.0000000000003847

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References 4:

Grant Support:

Keywords: Riboflavin Transporter Deficiency, Outcome Measure

Clinical Outcomes of Riboflavin Supplementation in Riboflavin Transporter Deficiency

Poster No:
P 062

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Introduction:
Riboflavin Transporter Deficiency (RTD) is a rare neurodegenerative disorder of childhood characterised by pontobulbar palsy, ataxia, respiratory insufficiency, limb muscle weakness and sensorineural deafness. Riboflavin supplementation has been shown to be beneficial in short-term reports but the quantum of benefit in various clinical domains is not well understood. The aim of this study was to conduct a review of clinical outcomes of riboflavin supplementation in patients with RTD.

Methods:
A PubMed search was conducted which identified 94 genetically confirmed cases of RTD who received riboflavin supplementation and had follow-up assessments. Information on the clinical and functional status before and after riboflavin supplementation was collected and analysed.

Results:
Seventy-six of the ninety-four individuals (80.9%) showed an overall improvement after riboflavin supplementation, and the remaining (19.1%) were stable, though some patients had deteriorations in individual domains with no reported deaths. The domains that had the highest rates of response to riboflavin supplementation were gross motor function (93.3% improved), bulbar palsy (91.3%), and ataxia (90.0%). Of the thirteen individuals with severe or profound hearing loss prior to riboflavin supplementation, four (25%) improved, eight had stable hearing, and one progressed from severe to profound. Eleven of twenty-eight (39.3%) had poor gross motor function (defined as having a Gross Motor Function Classification System rating of III to V) post-riboflavin supplementation, an improvement from the twenty-nine of thirty-six (80.6%) individuals pre-riboflavin. Three gastrostomies and eight tracheostomies were removed after riboflavin therapy. Ten of sixteen individuals (62.5%) with hearing loss had severe or profound hearing loss at follow-up. Two individuals remained tracheostomy-dependent.

Conclusions:
Riboflavin supplementation is a life-saving intervention for individuals with RTD which offers profound improvement in several functional domains, and early diagnosis improves outcomes. However, despite treatment, patients are left with residual disability. There is a need to accurately measure functional outcomes in children with RTD and develop additional disease modifying therapies.

References:
No

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References 2:

References 3:

References 4:

Grant Support:

Keywords: Riboflavin Transporter Deficiency, Outcome, Riboflavin

A deletion encompassing exons 4 and 5 of the PMP22 gene causes CMT1 with cranial neuropathy and marked facial diplegia

Poster No:
P 063

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Introduction:
PMP22 related neuropathies are generally due to either a 1.5Mb duplication leading to a demyelinating sensorimotor neuropathy known as Charcot-Marie-Tooth 1A (CMT1A), or a deletion of a similar 1.5Mb region causing a hereditary neuropathy with liability to pressure palsies (HNPP). Rarely, point mutations can cause either of these two phenotypes. Moreover, facial diplegia are rarely reported in CMT, especially in CMT1A.

Methods:
We report two members from one French family with CMT1 and facial diplegia carrying a small deletion in the PMP22 gene. We review the literature for other reports of facial weakness and CMT1A.

Results:
We present the clinical, electrophysiological and muscle MRI phenotype of two siblings with a demyelinating sensorimotor neuropathy and facial diplegia. The patients were found to carry a deletion encompassing exons 4 and 5 of the PMP22 gene [c.(178+1_179-1)_(*483_ ?)del]. A complete diagnostic work-up including a large panel of genes involved in CMT excluded an alternative diagnosis. The father also presented a neuropathy but had died before genetic testing. The segregation analysis confirmed that asymptomatic members in the family did not carry this deletion. PMP22 mRNA sequencing obtained from fibroblast of the proband is been currently performed. Three previous publications (Ionasescu et al., 1996; Werheid et al., 2016; and Ngappa et al., 2020) report some degree of facial weakness associated a mutation in the PMP22 gene, however, this is the first detailed report of two CMT1A patients with marked facial diplegia.

Conclusions:
This family broadens both the clinical and genetic spectrum of neuropathies associated with PMP22 point mutations and highlights the need to search for structural variations in the PMP22 gene in CMT1 patients with cranial nerve involvement.

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Yes

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References 4:

Grant Support:

Keywords: Charcot-Marie-Tooth, PMP22, facial diplegia, structural variations

Patients as Partners in Research

Poster No:
P 064

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Introduction:
Charcot-Marie-Tooth disease (CMT) is a hereditary motor and sensory neuropathy affecting 1 in 2500 people, approximately 3 million world-wide. A quality improvement initiative was launched in 2018 with a goal of advancing CMT research through the collection of patient reported data. The initiative aims to engage the patient community in research, the development of treatments, and ultimately a cure, for CMT. This is the first publication of this patient reported data.

Methods:
Data was collected via secure online questionnaire and anonymized prior to analysis.

Results:
By October 2022, 6091 individuals had created a patient reported data profile. Analysis of the anonymized data shows average (mean) age is 47.7 years (SD 22.3, range 8 months to 105 years, n=1961). 5911 individuals (97%) shared data on CMT type, distributed as, Type 1 35.3% (n=2085), Type 2 16.6% (n=980), Type X 4.3% (n=252), Type 4 2.8% (n=167), HNPP 0.9% (n=53), GAN 0.03% (n=2) and 40.1% (n=2369) do not know their type. 4034 individuals (66%) shared data on CMT subtype, 47 different sub-types are represented. The largest subtype groups are CMT1A 39.4% (n=1590), CMT2A 7.4% (n=297), CMT1X 5.1% (n=204), CMT1B 4.2% (n=170), CMT4C 1.6% (n=63) and 32.0% (n=1291) reported undiagnosed/unknown. Average (mean) age at diagnosis is 31.9 years (SD 20.9, range 0 to 81 years, n=1494).

Conclusions:
This initiative represents one of the largest available collections of CMT patient reported data, it is a valuable tool for patient engagement, research and clinical trial recruitment. We will present a summary of the anonymized data, real-world examples of how the initiative has supported CMT research and highlight opportunities for research collaboration. Additional questions will be added to the profile questionnaire during 2023 addressing gaps in CMT data, newly available data will be presented at PNS.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: This work was supported by the Charcot-Marie-Tooth Association.

Keywords: CMT, Charcot-Marie-Tooth, questionnaire, patient reported data

Diagnostic yield of a NGS panel in Brazilian patients with sporadic peripheral neuropathy

Poster No:
P 065

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Introduction:
The etiology of sporadic peripheral neuropathy (PN) remains unclear in many patients. In European and North American surveys, genetic causes have been increasingly recognized in these patients. Little is known about Latin American populations. Herein, we attempted to assess the diagnostic yield of a comprehensive NGS panel in Brazilian patients with PN without family history. We also explored potential predictors of an underlying genetic etiology in this cohort.

Methods:
We evaluated 41 consecutive adult patients regularly followed with PN and negative family history of PN or other neurological disorders as well as unclear etiology despite extensive laboratorial/neurophysiological (NCS+EMG) work-up. All patients then underwent genetic testing using a comprehensive next generation sequencing (NGS) panel that included 72 genes known to cause PN. Exclusively pathogenic or likely pathogenic variants according to American college of medical genetics and genomics (ACMG) criteria were retrieved. For each subject, we recorded demographic, clinical and NCS+EMG data. Such variables were then compared between positive vs negative NGS subgroups using Fisher exact test ($p<0.05$).

Results:
Fifteen patients had diagnostic NGS results (8 men, median age=43 years old), whereas 26 patients (15 men, median age = 47 years old) had negative or inconclusive results. Diagnostic yield of the PN panel was 15/41 = 36.5% in this Brazilian cohort. Seventeen distinct variants were found in 5 different genes; PMP22 and SH3TC2 were the most frequently identified. Earlier age of PN onset ($p = 0.013$), demyelinating pattern on NCS+EMG ($p = 0.021$) and presence of distal atrophy on clinical examination ($p = 0.043$) were all associated with positive NGS results.

Conclusions:
A significant proportion of Brazilian patients with sporadic PN has genetic etiology. NGS emerges as a diagnostically useful tool for adults with idiopathic PN, particularly when there is earlier age at onset and demyelinating features.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Next generation sequencing, Diagnosis, CMT

The eyes as a key to the diagnosis of a genetic neuropathy

Poster No:
P 066

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Introduction:
The etiological investigation of chronic axonal sensorimotor polyneuropathy (SMP) is broad, including multiple genetic entities. Some clinical details can be the key to the diagnosis.

Methods:
A case report.

Results:
A 58-year-old male was referred to the Neurology clinic due to progressive imbalance and lower limb numbness, for 8 years. He had a history of reasonably controlled diabetes mellitus (for five years) and 'congenital strabismus'. Family history included the father with familial amyloid polyneuropathy, a 35-year-old daughter with 'congenital strabismus' and distal lower limb hypoesthesia. On neurological examination, the patient had bilateral exotropia and supraversion limitation, bilateral reduced pain and proprioceptive sensation to the ankle, globally hypokinetic osteotendinous reflexes, bilateral Babinski's sign, cavus foot, Romberg's sign, and wide-based gait, needing unilateral support. The patient denied dysautonomia complaints. Nerve conduction studies revealed severe chronic axonal SMP, and the brain MRI was unremarkable. Common causes of acquired chronic polyneuropathy were excluded, and the transthyretin genetic study was normal. Suspecting a genetic etiology, a hereditary axonal neuropathy panel was performed, revealing a heterozygous pathogenic variant (c.1249G>A) in the TUBB3 gene. This variant causes axonal SMP associated with congenital fibrosis of the extraocular muscles type 3. Additional familial investigation revealed the same neurophysiologic characteristics and variant in the older daughter.

Conclusions:
Oculomotor symptoms are not always considered in the differential diagnosis of axonal SMP, especially when the former are congenital and not progressive. This case highlights the importance of considering all clinical findings, albeit unlikely connected, for an accurate diagnosis.

References:
Yes

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References 2:
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3. Leandro-García LJ, Leskelä S, Landa I, et al. Tumoral and tissue-specific expression of the major human beta-tubulin isotypes. Cytoskeleton (Hoboken, NJ). 2010;67(4):214-223.

References 4:
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Grant Support:

Keywords: chronic axonal sensorimotor polyneuropathy, TUBB3 gene, congenital fibrosis of the extraocular muscles type 3, genetic, brain MRI

Clinical And Neurophysiological Characteristics Of A Brazilian Cohort Of Patients With SH3TC2 Related HSMN

Poster No:
P 067

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Introduction:
Charcot-Marie-Tooth neuropathy type 4C (CMT4C) is an autosomal recessive demyelinating neuropathy caused by mutations in the SH3TC2 gene. Patients usually presents in first decade of life with distal weakness and sensory impairment, areflexia, foot and spine deformities and sometimes cranial nerve involvement or respiratory distress. We sought to describe a Brazilian cohort of patients with confirmed diagnosis of CMT4C, highlighting electrophysiological data.

Methods:
Eight individuals from 6 families were analyzed. Clinical and electrophysiological data were retrospectively collected from clinical records. Sex, age of onset, presenting symptom and electrophysiological data were collected for further analysis.

Results:
Six out of 8 patients (75%) were female. Frequent falls and difficulty walking were the most common initial features in up to half of the patients. In 6 patients (75%), symptoms started in the first decade of life. Interestingly, nerve conduction studies revealed a non-uniform reduction of conduction velocity and temporal dispersion in all of the patients.

Conclusions:
The presence of temporal dispersion in all studied patients may suggests that SH3TC2 play an important role in peripheral nerve maintenance. Indeed, recently, nerve pathology from SH3TC2-knockout animal models revealed loss of internodal architecture that could ultimately explain this feature. Temporal dispersion might be a frequent finding in CMT4C patients nerve conduction studies, which may aid in differentiation with others CMTs subtypes. Clinicians must be aware of this to avoid extensive investigation and misdiagnosis with acquired neuropathies.

References:
Yes

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References 4:

Grant Support: ICGNMD Consortium group

Keywords: CMT, Neurophysiology, SH3TC2

Brazilian Family with X-linked Charcot-Marie-Tooth disease type 6 related to p.R158H mutation in the PDK3 gene

Poster No:
P 068

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Introduction:
X-Linked Charcot-Marie-Tooth disease type 6 (CMTX6) is a very rare condition caused by mutations at the PDK3 gene. The only 3 families described have distinct origins (Australian, Korean, and Germanic), and the following variants: R158, R158 and H168N. We describe a large Brazilian family with a new mutation.

Methods:
Clinical and electrophysiological evaluation. Exome sequencing of the proband followed by segregation studies.

Results:
We found 9 affected members, including 6 females and 3 males, Males presented a severe motor and sensory axonal neuropathy of earlier onset (first decade) absent tendon jerks and pes cavus, while most females presented a very mild disease at later ages. Pain was a frequent manifestation. Whole exome sequencing showed the c.485G>A (p.R162H) variant in the PDK3 gene, that segregated with the disease and was absent in 12 asymptomatic members.

Conclusions:
Here we describe a Brazilian family with CMTX6 carrying a previously non reported variant in the PDK3 gene that segregates with the disease. Interestingly, the clinical presentation seems to be very similar in all 3 families whose clinical description is available, including ours. Additionally, all 3 described mutations are located very close, suggesting that they may result in similar functional abnormalities.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Charcot-Marie-Tooth

Synaptic Dysfunction And Structural Alterations At The Neuromuscular Junction In Mouse Models Of Neuromuscular Disease

Poster No:
P 069

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Introduction:
The neuromuscular junction (NMJ) is the critical synapse for functional muscle contraction. NMJ dysfunction is present or implicated in multiple neuromuscular diseases, including peripheral neuropathies. Here we investigate multiple mouse models of rare neuromuscular disorders to assay the NMJ, laying groundwork for future mechanistic and preclinical studies.

Methods:
We are using repetitive nerve stimulation (RNS) to measure EMG decrement and immunofluorescence to assess NMJ anatomy in proximal and distal muscles. Mouse models including Nadk2 (neurodegenerative), Pla2g6 (INAD), Nefl (CMT2E), and Gjb1 (CMT1X) will be evaluated at pre- and post-onset disease stages .

Results:
Data acquisition and analysis in these models is in progress. Preliminary RNS data in Pla2g6 and Nadk2 mice show normal whole-muscle function at pre-onset ages (4 weeks), but EMG decrement is present at later time points (13 weeks and 5 weeks, respectively), suggesting NMJ dysfunction develops with disease progression. Pla2g6 mice show anatomical changes at the NMJ, including fragmentation of the postsynaptic sites, partial innervation by nerve terminals, and axonal spheroids in motor axons. The time course and spectrum of these changes is being evaluated. Published work found approximately half of the pre-synaptic nerve terminals have recently retreated from the NMJ at 5 weeks in Nadk2 mice [1], consistent with the onset of EMG decrement between 4 and 5 weeks. Pre-synaptic release defects at the NMJ have been previously established in the related Gars (CMT2D) mice [2], providing a basis for comparison with the studies described here.

Conclusions:
Mouse models with interesting NMJ dysfunction in RNS and immunofluorescence will be evaluated in more detail using two-electrode voltage clamp at individual NMJs and possibly transmission electron microscopy. This data will determine whether deficits occur in the pre- or post-synaptic compartment and will provide insight into molecular mechanisms, as well as possible targets for therapeutics.

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Yes

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Grant Support:

Keywords: Electromyography, Neuromuscular Junction, Peripheral Neuropathy

Beclin-1 Ablation in Schwann Cells Leads to Severe Demyelinating Peripheral Neuropahty

Poster No:
P 070

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Introduction:
Beclin-1 protein takes part in different protein networks, thus switching its role from supporting autophagy induction to regulating autophagosome maturation and endosomal trafficking. The protein is essential for embryonic development and its dysregulation is linked to several human pathologies, including cancer and neurodegenerative diseases. However, while assessed in neuronal populations, astrocytes and microglia, its role was far less investigated in myelinating glia. Schwann cells (SCs) are responsible for myelin production in the peripheral nervous system and fundamental for its proper development and function. Recent findings point at an emerging role of autophagy in regulating SC maturation and homeostasis and in myelin clearance in injured nerves; moreover, a dysregulation of the autophagic flux and the endosomal trafficking emerged as potential pathophysiological mechanisms underlying Charcot-Marie-Tooth peripheral neuropathies.

Methods:
To gain further knowledge in these aspects, we generated a new SC-specific Becn1 knockout mouse line (SCBecn1KO).

Results:
SCBecn1KO mice develop a severe peripheral neuropathy, with involuntary tremors and progressive motor impairment, leading to the loss of the ability to walk properly and to grab or stand on a grid. This functional degeneration is accompanied by a marked body weight loss, muscle atrophy and premature death. SCBecn1KO mice display an extensive demyelination, detectable since post-natal day 3, and worsening over time, becoming almost complete in adults. Moreover, ultrastructural analysis revealed radial sorting impairment and the presence of enlarged SC cytoplasm, with progressive accumulation of intracellular vesicles. Interestingly, transcriptomic analysis of pups and 2-month-old peripheral nerves highlighted in SCBecn1KO samples a pro-mitotic alteration of cell cycle, sustained also by immunofluorescence experiments, together with impaired nervous system development, neurite outgrowth and muscular contraction.

Conclusions:
Further characterization of this mouse model will pave the way for a deeper understanding mechanism underlying SC development and points to Beclin-1 and its binding partners as novel candidate genes for recessive CMT forms.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Beclin-1, Schwann cells, Peripheral neuropathy, Demyelination, Endosomal trafficking

A dose-escalation and safety study of AAV9-mediated gene replacement therapy for the treatment of CMT4C

Poster No:
P 071

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Introduction:
Charcot-Marie-Tooth disease type 4C (CMT4C) is a demyelinating neuropathy caused by loss of function mutations in the SH3TC2 gene, that ishighly expressed in myelinating Schwann cells. We previously developed a therapeutic AAV9-miniMpz.SH3TC2.myc vector for Schwann cell-targeted replacement of SH3TC2 leading to functional and morphological improvements in the Sh3tc2-/- model of CMT4C. Here, we generated and tested a clinical stage vector by introducing a minimal human MPZ promoter driving expression of SH3TC2 to treat CMT4C.

Methods:
Groups of 1-month old Sh3tc2-/- mice were treated with 3 different doses (4e10, 1.2e11, and 3.5e11 vg) of AAV9-hum-miniMpz.SH3TC2-SV40pA or the mock vector (AAV9-hum-miniMpz.EGFP) by lumbar intrathecal injection. Outcomes were compared by behavioral, electrophysiological and morphological analysis 8 weeks post injection. Additional groups injected with the 3 different vector doses or with saline were evaluated for tissue integrity and inflammatory responses.

Results:
The mid and high vector doses provided adequate biodistribution to the peripheral nerves and high rates of cell-specific therapeutic gene expression in Schwann cells, resulting in significant and consistent across different outcome measures therapeutic benefits in the CMT4C model 8 weeks post injection. Treated mice showed improved motor performance in grip strength and rotarod testing as well as motor nerve conduction velocities. Morphological analysis revealed significant improvement in g-ratios, myelin thickness and ratios of demyelinated fibers in lumbar roots and femoral nerves of treated Sh3tc2-/- mice. In contrast, the low dose only benefited electrophysiological outcomes without behavioral or morphological improvement. None of the tested vector doses caused any significant tissue toxicity or immune reactions in neural tissues or peripheral organs.

Conclusions:
This study provides proof of principle for dose-dependent effectiveness and safety of intrathecal AAV9-mediated gene replacement therapy to improve functional outcomes and myelin pathology in the Sh3tc2-/- model of CMT4C, which is relevant for the treatment of CMT4C patient.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: Neurogene Inc.

Keywords: CMT, AAV9, Gene therapy

Clinical, Electrophysiological And Radiologic Profile of Hirayama Disease From a Tertiary Care Institute in India

Poster No:
P 072

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Introduction:
Cervical flexion induced myelopathy (CFIM) or Hirayama disease (HD) is a lower motor neuron (LMN) disorder manifested as distal upper limb amyotrophy. There is a lack of knowledge among clinicians due to its rarity. This study aims to review clinical, electrophysiological and radiologic characteristics of HD patients.

Methods:
Patients with clinically suspected HD between 2018 and 2022 were reviewed. Search criteria included insidious onset progressive pure motor LMN weakness of unilateral or bilateral distal upper limbs, electromyography (EMG) showing chronic denervation in C7-T1 myotomes, and dynamic cervical magnetic resonance imaging (MRI) suggesting HD like anterior dural displacement, asymmetric cord flattening/atrophy, cord hyperintensity, epidural flow voids and epidural crescent enhancement. Clinical, electrophysiologic and MRI data were were analysed using SPSS software 26.0.

Results:
Ninety-six patients met the diagnostic criteria for HD. 99% were males. Mean age was 21.3 years. Average age of symptom onset was 18 years. Median duration of symptoms prior to presentation was 3 (2-4) years. All had progressive distal upper limb weakness and wasting. Fourty-six (48%) had unilateral and the rest (52%) had asymmetric bilateral involvement. Family history was confirmed in one. Cold paralysis, oblique atrophy and polyminimyoclonus were seen in 70 (73%), 95 (99%) and 55 (57%) patients respectively. Anterior horn cell involvement on EMG were noted in affected limb in all patients and unaffected limb in 17 (37%) patients. Dynamic MRI revealed anterior dural displacement in 91 (95%) patients, cord atrophy in 74 (77%), asymmetric flattening of cord in 84 (87.5%), cord hyperintensity in 42 (44%) and epidural flow voids in 68 (71%) patients. Contrast MRI was performed in 33 (34.3%) patients of which 31 (94%) had epidural crescent enhancement. One underwent surgery.

Conclusions:
HD is self-limited, and needs to be differentiated from its mimics to establish correct treatment. Dynamic MRI clinches the diagnosis.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Hirayama Disease, Electrophysiology, Flexion MRI

Serum Big Tau in Charcot Marie Tooth: A candidate biomarker for PNS damage

Poster No:
P 073

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Introduction:
Big tau is a peripheral isoform of tau and it is expressed mainly in the adult peripheral nervous system (PNS), but also in adult neurons of the central nervous system (CNS) that extend processes into the periphery. The role of big tau as a biomarker in PNS conditions is still unknown. We sought to address this challenge by generating an anti-tau antibody that selectively binds to peripherally expressed 'big tau' isoform and avoids the brain-derived tau isoform. We evaluated the performance of a novel big tau assay in blood-based cohort of patients with different variants of Charcot Marie Tooth (CMT) due to its heterogeneity in pathophysiology.

Methods:
Methods: We measured levels of big tau in serum in a cohort of patients diagnosed with CMT (n= 58) and compared with a group of controls (n= 33). We compared the mean values in the different subtypes of CMT to see if there was a significant difference between subgroups. Group differences were examined using the Mann-Whitney test (two categories) or the Kruskal-Wallis test with Dunn's multiple comparison (three or more groups).

Results:
The statistical analysis showed a significant difference between CMT and controls (p= 0.008). Furthermore, when dividing CMT cases into subgroups (Kennedy; BICD2; GJB1 and PMP22 dup) Levels of serum big tau in CMT patients with PMP22 mutation were significantly higher compared to the other subgroups (p=<0.05).

Conclusions:
Our results show that levels of big tau in serum are significantly increased in patients with CMT compared to controls. The PMP22 mutation was associated with significantly higher big tau concentration in the CMT group. Big tau is a potential candidate for PNS conditions and might complement other PNS markers such as NfL. The clinical and biological role of Big tau in PNS conditions is still unknown and require further research

References:
No

References 1:

References 2:

References 3:

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Grant Support:

Keywords: CMT, Big Tau, Biomarkers

Neuromuscular Junction Transmission Dysfunction in Patients with Charcot-Marie-Tooth Disease − The ESTABLISH Study

Poster No:
P 074

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Introduction:
Charcot-Marie-Tooth (CMT) disease is a hereditary peripheral nerve disorder characterized by debilitating sensory and motor symptoms with no approved treatments. Preclinical studies and evidence from other neurogenic disorders suggest that neuromuscular junction (NMJ) transmission dysfunction is a disease mechanism contributing to clinical symptoms and deficits in CMT, however this remains to be studied in patients.

Methods:
The primary aim was to investigate NMJ transmission in CMT patients vs. healthy age-matched controls (HC) using electrophysiological tests (single fibre electromyography and repetitive nerve stimulation). Secondary aims included assessment of test-retest reliability and tolerability of electrophysiological and clinical tests (6-minute walk test, dynamometry, manual muscle testing, 6-spot step test, 10-meter walk/run test, berg balance scale, timed up-and-go, 9-hole peg test) in CMT. As an exploratory aim, correlations between electrophysiological and clinical outcomes in CMT were investigated. CMT patients underwent repeated electrophysiological and clinical testing at four visits. HC underwent electrophysiological testing at one visit.

Results:
A total of 21 CMT patients (46.4±14.4 years) and 10 HC (43.3±12.7 years) were enrolled at two centres. Jitter, a measure of NMJ transmission variability, was higher in CMT (median: 56.3µs (range: 35.3;196.6µs) vs. HC (median: 29.4µs (range: 18.6;35.6µs) ($p<0.05$). Blocking, a measure of NMJ transmission failure, was higher in CMT (median: 13.4% (range: 0.0;90.9%) vs. HC (median: 0.0% (range: 0.0;4.5%) ($p<0.05$). In CMT, jitter and blocking correlated with strength, mobility, fatigue and balance. Jitter and blocking were greater in CMT type 2 vs. CMT type 1. All clinical tests were well tolerated and showed moderate to excellent reliability (ICC: 0.52-0.97). Single fibre electromyography showed better sensitivity, tolerability and reliability than repetitive nerve stimulation.

Conclusions:
The ESTABLISH study demonstrates that 1) NMJ transmission dysfunction is evident in CMT patients and 2) NMJ transmission is linked to clinical deficits warranting investigation of drugs targeting NMJ transmission for treatment of CMT.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: NMD Pharma A/S sponsored the study

Keywords: Charcot Marie Tooth Disease, Single Fiber EMG, Neuromuscular Junction Transmission, Outcome Measures, Electrophysiology

Surgical Release of Ulnar and Median Nerves in CMT1A: Prevention and Treatment of a Second Hit

Poster No:
P 075

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Introduction:
Peripheral nerves in patients with CMT1A are diffusely enlarged and areas of potential compression at the carpal tunnel (CT or CTS referring to syndrome), elbow (cubital tunnel or CuT), and Guyon's canal (GC) can be released to reduce the risk of a 'second hit' (nerve injury due to compression) in the setting of their genetic, progressive neuropathy, however there is little data on the efficacy and timing of surgical nerve decompression.

Methods:
Six genetically diagnosed and suspected CMT1A patients were reviewed that reported hand symptoms in clinic in 2021-2022, obtained electrophysiologic data, and were evaluated by neurosurgery for surgical decompression of the CT, CuT, and GC.

Results:
All patients had severe slowing of motor nerve conduction velocities and absent sensory responses on NCS consistent with CMT1A. Electrographic CTS (discrepantly prolonged DML or reduced amplitudes) occurred bilaterally in 83% (5/6). Electrographic bilateral GCS and unilateral CuTS were observed in 33% (2/6) of patients. Three patients with sonographic data all demonstrated diffuse enlargement of the ulnar and median nerves at the forearm (mean cross-sectional area, CSA=20 mm2 and 26 mm2). Focal narrowing occurred at the CT in two patients (mean CSA=11.2 mm2 vs 37 mm2 at the forearm). One patient underwent unilateral, and two patients underwent bilateral decompression at the CT, CuT, and GC with a follow-up time of 8 months and 2 months. Two patients endorsed significant improvement of gross grip strength in at least one hand and resolution of median sensory abnormalities in territories of released nerve, one patient had stabilization of symptoms.

Conclusions:
Although altered due to the nature of their CMT1A, electrophysiologic and sonographic data provided focal findings in our patients with hand symptoms. Patients who underwent surgical decompression had symptomatic benefits. These releases can reduce the risk of a 'second hit' of neurologic injury due to compression.

References:
Yes

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Grant Support:

Keywords: Charcot Marie Tooth Disease type 1A, Compressive neuropathy, carpal tunnel syndrome, ulnar neuropathy, Charcot Marie Tooth

The Importance of Evaluating Family Members

Poster No:
P 076

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Introduction:
Despite expanding molecular testing technology and increasing access to genetic testing, many individuals and families with neuromuscular conditions still experience a diagnostic odyssey. Molecular diagnosis allows personalized clinical surveillance and treatment, including access to a growing number of targeted treatments specific to the diagnosis1,2,3,4. Predictive testing also becomes an option for healthy family members. The heterogenous nature of neuromuscular conditions and expanding genotype–phenotype correlations can make confirming a molecular diagnosis challenging. Including family members, when available, in the diagnostic work up of hereditary neuromuscular conditions can provide a better diagnostic yield for rare or never previously reported gene variants.

Methods:
We present a family with autosomal dominant limb-girdle weakness with late-teen or young adult onset and hearing loss. Electromyogram and muscle biopsy have both neuropathic and myopathic features. Genetic testing for multiple conditions has been completed on two family members including single gene analysis, deletion/duplication analysis, methylation studies, DNA repeat analysis, and next generation sequencing panels. A candidate heterozygous variant in BSCL2 (c.921del; p.Thr308Glnfs*28) was identified in proband. Trio whole genome sequencing will be undertaken for a comprehensive approach to molecular diagnosis.

Results:
The candidate heterozygous variant in BSCL2 (c.921del; p.Thr308Glnfs*28) segregated with three affected family members but evidence remains insufficient to conclude pathogenicity for dominant disease. The presumed loss-of-function variant would typically indicate carrier status. Whole genome sequencing with reflex to RNA sequencing is expected to provide additional candidate genes or establish a genetic diagnosis by utilizing comprehensive genome-wide analysis and all available and informative family members.

Conclusions:
Including family members in comprehensive genomic evaluation and interpretation provides the highest probably of identifying the molecular etiology, and thus focused management and counseling.

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Yes

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Grant Support: The Inherited Neuropathy Consortium is part of the NIH Rare Diseases Clinical Research Network (grant #1U54NS065712-01). The INC also receives funding from the Muscular Dystrophy Association and the Charcot-Marie-Tooth Association.

Keywords: genome

Update on Genetic Testing Strategies and Genetic Counseling for Charcot Marie Tooth Disease in the United States

Poster No:
P 077

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Introduction:
Hereditary peripheral neuropathy, or Charcot Marie Tooth disease (CMT), is one of the most common neurogenetic diseases, affecting at least 1 in 2,500 people. More than 100 causative genes have thus far been identified. Establishing a molecular diagnosis is vital to involvement in research for targeted treatments, offering predictive testing options for family members, family planning option counseling and neurotoxic drug avoidance1. Given the complexities of a growing number of identified genetic causes, widening phenotypic spectrums, and technological advancements and availability of comprehensive genomic analysis, updated guidelines are necessary. The Inherited Neuropathy Consortium (INC) will provide updated best practice guidelines for clinical genetic testing2 and genetic counseling3 for CMT.

Methods:
Literature review will identify available clinical genetic testing options, current and pending targeted treatments, genetic counseling and testing strategy recommendations, and current limitations to providing accurate molecular diagnosis. A focus group of neurogenetic counselors, neuromuscular specialists, and molecular scientists will review, access, and provide updated recommendations for clinical genetic counseling and testing for CMT.

Results:
Next generation sequencing changed the landscape of genetic testing and how it is offered but PMP22 deletion/duplication continues to be best practice as the first line test for those with demyelinating neuropathy. For people without electrodiagnostic results or axonal neuropathies, or for those with negative PMP22 copy number testing, panel testing is the most common next step.

Conclusions:
Panel testing for CMT will not identify patients with some forms of CMT, such as those with SORD neuropathy or RFC1-spectrum disorder. Therefore, exome or genome testing utilizing long-read sequencing should be considered in this patient population and used when panel testing does not yield a diagnosis. Families should undergo genetic counseling with positive results to discuss implications of testing results, or for next steps with negative or variant of uncertain significance results.

References:
Yes

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References 4:

Grant Support: The Inherited Neuropathy Consortium is part of the NIH Rare Diseases Clinical Research Network (grant #1U54NS065712-01). The INC also receives funding from the Muscular Dystrophy Association and the Charcot-Marie-Tooth Association.

Keywords: CMT, genome, hereditary neuropathy

Phenotype Variability in Patients with Dynamin-2 (DNM2) Mutations

Poster No:
P 078

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Introduction:
Charcot–Marie–Tooth (CMT) disease and related disorders are clinically and genetically heterogeneous. Over 100 causative genes have been identified including Dynamin-2 (DNM2), a type of guanosine triphosphatase that is involved in multiple cellular functions including endocytosis, membrane trafficking, actin assembly and centromere cohesion. DNM2 variants are commonly associated with intermediate CMT and CMT2 as well as centronuclear myopathy, congenital contracture syndrome type 5 and hereditary spastic paraplegia implying phenotypic variability. The phenotypic spectrum is evolving as new variants are identified. Aim: We report 5 patients with DNM2 related neuropathy and expand the associated clinical phenotype.

Methods:
All genetically confirmed cases of DNM2 in our cohort were retrospectively included. Clinical features, variant type and electrophysiological data were extracted and analysed.

Results:
From our cohort we identified 5 patients. 4/5 were females. 2 patients had a family history of CMT and 3 were apparently sporadic. Symptoms appeared in the first 2 decades (Range 7-20 years) and Charcot-Marie-Tooth Examination score ranged from 4 to 12. Clinical examination revealed neuropathy alone in 4 patients, and the fifth patient had a combination of neuropathy and myopathy (clinically and neurophysiologically). Novel variants were as follows; c.1736T>C p.(Phe579Ser), c.1733G>A p.(Gly578Asp) and c.1660A>G p.(Lys554Glu). Segregation was confirmed for the latter 2. Although both neuropathy and myopathy have been described with different DNM2 variants, we report a patient with a combined phenotype of neuropathy and myopathy with a c.1463 p.(Thr488Arg) missense variant.

Conclusions:
DNM2-related diseases are phenotypically heterogeneous. Although both neuropathy and myopathy have been described with DNM2 variants it is important to actively look for both in CMT patients with EMG, which is an essential part of the neurophysiological examination.

References:
Yes

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Chen S, Huang P, Qiu Y, Zhou Q, Li X, Zhu M, Hong D. Phenotype variability and histopathological findings in patients with a novel DNM2 mutation. Neuropathology. 2018 Feb;38(1):34-40. doi: 10.1111/neup.12432. Epub 2017 Oct 3. PMID: 28971531.

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References 3:

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Grant Support:

Keywords: Charcot Marie Tooth, Dynamin 2, Novel variant

Pathophysiological mechanisms in a new form of Charcot Marie Tooth due to a mutation in PDXK

Poster No:
P 079

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Introduction:
Charcot Marie Tooth (CMT) disease is the commonest inherited group of neuromuscular diseases. This group of diseases, affecting the peripheral nervous system, is characterized by wide clinical and genetic heterogeneity, with around 100 genes identified to date. Here, we describe 4 new patients, from two consanguineous Middle Eastern families, presenting with a rare subtype of CMT, due to a homozygous missense p. Ala228Thr mutation in PDXK, previously described by Chelban et al 2019. While the patients described by Chelban et al are affected with AR axonal CMT associated with visual loss, our patients have demyelinating CMT and no visual impairment. Here, we used patients' cells, including hiPSC-derived Motor Neurons (hiPSC-MN) to study the pathomechanisms in this new form of CMT.

Methods:
We evaluated the levels of PDXK by QRT-PCR and Western-Blot in the different cell types used the Multi Electrode Array (MEA) technology on hiPSC-MNs to assess potential electrical defects in patients.

Results:
In patients' lymphocytes and hiPSCs, we have found 40% decrease in PDXK protein levels. Interestingly, in patient's hiPSC-MNs, we observed no such decrease. At the mRNA levels no significant differences were identified suggesting a post-translational degradation of PDXK. Using MEA technology, we studied the general electrical activity of hiPSC-MNs by measuring Action Potential frequencies and amplitudes. Our preliminary results suggest increased global electrical activity in patients' hiPSC-MNs, as compared to controls. These results will be completed by additional measurements in hiPSC-DRG neurons, but they are very encouraging toward using hiPSC-derived neurons from the PNS to study the pathogenicity of mutations in this specific subtype of CMT and in CMT in general.

Conclusions:
Here, we describe new patients with the homozygous p. Ala228Thr mutation in PDXK. Interestingly, our patients present a very different phenotype and our preliminary results from MEA technology suggest that our model enables to study this phenotypical variability.

References:
Yes

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PDXK mutations cause polyneuropathy responsive to pyridoxal 5'-phosphate supplementation Chelban et al.Ann Neurol . 2019 Aug;86(2):225-240. doi: 10.1002/ana.25524

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References 4:

Grant Support:

Keywords: charcot-Marie-Tooth, PDXK, Multi Electrode Array, hiPSC Motor Neurons, phenotypical variability

Evaluating therapeutic potential of SARM1 inhibition in mouse models of CMT

Poster No:
P 080

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Introduction:
Inhibiting SARM1 has been shown to be axon protective in mouse models following challenges including injury, chemotherapy-induced neuropathy, and diabetic/metabolic neuropathy. Studies breeding knockout Sarm1 rats to a model of Mfn2/CMT2A also showed benefit. Here we test whether inhibiting SARM1 is effective in several other mouse models of Charcot-Maire-Tooth disease (CMT).

Methods:
We have bred Sarm1 knockout mice to Gjb1/CMT1X, Kif1A/HSN2, and Fig4/CMT4J mouse models. In addition, mouse models of Gars/CMT2D, Ighmpb2/CMT2S, and Nefl/CMT2E are currently being dosed with a SARM1 dominant negative AAV (dn-SARM1-AAV) at birth. Mice are then evaluated through body weight, grip strength, neurophysiology, and histopathology.

Results:
The knockout of Sarm1 in Kif1A/HSN2C, Fig4/CMT4J, and Gjb1/CMT1X did not significantly alter disease progression by any of our outcome measures. Using dn-SARM1-AAV in positive control studies of sciatic nerve crush showed that, histologically axon integrity was protected, but functionally, there was no EMG following distal nerve stimulation. Treatment and evaluation of Gars/CMT2D, Ighmpb2/CMT2S, and Nefl/CMT2E mouse models of CMT is ongoing.

Conclusions:
SARM1 inhibition in mouse models of HSN2C, CMT4J, and CMT1X has no overt benefit and does not alter disease pathology. Studies with dn-SARM1 AAV in additional models of CMT and in nerve injury are on-going.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: NINDS: R03NS123787-01A1

Keywords: SARM1, CMT, gene therapy

The role of ATF4 on the neuropathy phenotype of Charcot-Marie-Tooth disease type 2D mouse models.

Poster No:
P 081

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Introduction:
The integrated stress response (ISR) is activated in motor neurons of mouse models of tRNA synthetase-associated Charcot-Marie-Tooth disease (CMT). The ISR precipitates two major cellular consequences – shutdown of cap-dependent translation and ATF4 target gene expression. While inhibition of the ISR with a drug targeting the activating kinase, Gcn2, was highly beneficial, it is unclear whether the neuropathy phenotype is due to decreased translation, or expression of ATF4 targets.

Methods:
To determine the role of ATF4 expression in CMT2D, we have generated mice that overexpress ATF4 specifically in motor neurons, and Gars/CMT2D mice with motor neuron-specific ATF4 knockout. Neuromuscular performance, nerve histology, ATF4 target-gene expression, and translation levels will be assessed in these mice.

Results:
Motor neuron-specific ATF4 overexpression causes changes consistent with those seen in CMT2D mice including decreased body weight, nerve conduction velocity (NCV), and latency to fall in an inverted wire hang test. Furthermore, homozygous, motor neuron-specific deletion of Atf4 from Gars/CMT2D mice appears to rescue the deficits in body weight and NCV (N = 2 mice). We are working to evaluate nerve histology, expression levels of ATF4 targets, and translation rates in these mice while increasing our sample sizes.

Conclusions:
The preliminary results shown here indicate ATF4 expression in motor neurons is detrimental to neuromuscular function and may be a feasible therapeutic target for CMT2D. While a larger sample size is needed for the Atf4 knockout experiments, it is promising to see such a dramatic effect on nerve physiology. The results of this project will refine our understanding of the pathomechanism underlying tRNA synthetase-associated CMT.

References:
Yes

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Spaulding EL, Hines TJ, Bais P, Tadenev ALD, Schneider R, Jewett D, Pattavina B, Pratt SL, Morelli KH, Hill DP, Gobet C, Pipis M, Reilly MM, Jennings MJ, Horvath R, Bai Y, Shy ME, Alvarez-Castelao B, Schuman EM, Bogdanik LP, Storkebaum E, Burgess RW. (202

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References 4:
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Grant Support: Uplifting Athletes Young Investor Draft w/ matching funds from the Charcot-Marie-Tooth Association to TJH. NINDS R37 NS054154 to RWB.

Keywords: GARS, CMT2D, ATF4, integrated stress response, tRNA synthetase

Motor Neuron Disease or Sensory Neuropathy? L-Serine as a modulating factor

Poster No:
P 082

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Introduction:
Hereditary Sensory Neuropathy Type 1 (HSAN1) is a progressive sensory neuropathy caused by mutations in the enzyme Serine-palmitoyltransferase (SPT). SPT catalyzes the rate-limiting step in the de-novo synthesis of sphingolipids. HSAN1 mutations induce a permanent change in the substrate specificity of SPT shifting from the canonical substrate L-Serine to the alternative L-Alanine. This forms an atypical class of neurotoxic 1-deoxySphingolipids. In contrast, amyotrophic lateral sclerosis (ALS) is a progressive, neurodegenerative disease affecting lower and upper motor neurons. Clinical hallmarks include progressive muscle atrophy, speech and swallowing difficulties, fasciculation, altered reflexes, and spasticity. Recently, we reported five heterozygous variants in SPT identified in eight unrelated families with childhood ALS.

Methods:
We analyzed the sphingolipid profile in blood of affected individuals and cellular models expressing the SPT-ALS variants by high-resolution mass spectrometry. We used stable isotope labelling to characterize activity of the mutants and their impact on sphingolipid de-novo synthesis.

Results:
Different from SPT variants that cause HSAN1, the dominantly-acting SPT-ALS variants cluster in exon 2. This domain is important for the interaction with the regulatory SPT subunit ORMDL3. Consequently, all SPT-ALS variants showed a reduced homeostatic control causing an excessive de-novo formation of ceramides and other SL species. Restricting the SPT substrate L-Serine, reduced the formation of canonical SL but caused an increased formation of 1-deoxySL instead. This indicated that low L-serine might cause a phenotypic shift from a motor to a sensory phenotype. This was confirmed in an SPT-ALS family which members showed either a sensory or a motor phenotype despite having an identical mutation.

Conclusions:
Mutations in SPT can either cause the sensory neuropathy HSAN1 or result in motor neuron degeneration and childhood ALS. Limiting L-serine availability causes a metabolic and phenotypic shift from the motor to the sensory phenotype.

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Yes

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Lone MA, Aaltonen MJ, Zidell A, et al. SPTLC1 variants associated with ALS produce distinct sphingolipid signatures through impaired interaction with ORMDL proteins. J Clin Invest 2022;132.

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Mohassel P, Donkervoort S, Lone MA, et al. Childhood amyotrophic lateral sclerosis caused by excess sphingolipid synthesis. Nat Med 2021.

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Grant Support: Swiss Science Foundation (SNF_32ER30_187505)

Keywords: peripheral neuropathy, sphingolipids, serine-palmitoyltransferase, L-serine, motor neuron disease

C698R Mutation in Lrsam1 Gene Impairs Nerve Regeneration in a CMT2P Mouse Model

Poster No:
P 083

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Introduction:
Missense mutation C694R in the RING domain of the LRSAM1 gene results in a dominantly inherited polyneuropathy, Charcot-Marie-Tooth disease type 2P (CMT2P). The C694R mutation altered the RNA-binding protein nuclear translocation likely by disrupting the protein–protein interaction between LRSAM1 and the RNA-binding proteins, a potential mechanism in CMT2P pathogenesis. To further explore this mechanism in vivo, we have generated a Lrsam1C698R knock-in mouse model, the amino acid substitution equivalent to the human C694R mutation.

Methods:
A Lrsam1C698R knock-in mouse model was produced through CRISPR/Cas9 technology. The C698R Lrsam1 knock-in mice were evaluated clinically using Rotarod and hindlimb clasping tests, physiologically by nerve conduction studies, and morphologically on nerve sections.

Results:
Both heterozygous (Lrsam1+/C698R) and homozygous (Lrsam1C698/C698R) knock-in mice displayed normal motor functions on behavioral tests as well as normal on nerve conduction studies. Axonal density and myelin thickness were not significantly different between mutants and wild-type mice by sciatic nerve morphometric analysis up to 17 months of age. In line with these normal findings, protein–protein interactions between mutant LRSAM1 and RNA-binding proteins (such as FUS and G3BP1) were still present in mouse cells, which differs from the disrupted interactions between these proteins in human CMT2P cells. However, after crush nerve injury, Lrsam1+/C698R mice had a mild, but statistically significant, reduced compound nerve action potential and conduction velocity during recovery.

Conclusions:
C698R mutation results in a mild impaired nerve regeneration in mice. While the phenotype is not robust, mild abnormality in nerve repair provides a helpful clue toward the slowly progressing polyneuropathy in CMT2P.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: National Institute of Neurological Disorders and Stroke (R01NS115748 and R01NS124813).

Keywords: Charcot-Marie-Tooth disease type 2P , Lrsam1, peripheral nerve regeneration , knock-in mouse, nerve conduction study

Two Mutations Causing Peripheral Neuropathy: Charcot Marie Tooth And Hereditary Transthyretin Amyloidosis

Poster No:
P 084

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Institutions:
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Introduction:
Hereditary transthyretin amyloidosis (ATTRh) is an autosomal dominant disease in which the systemic deposition of amyloidogenic mutant transthyretin causes multiorgan failure.Charcot marie's disease is another cause of hereditary neuropathy, which manifests as atrophy of the lower limbs, cavus feet and difficulty walking. A 43-year-old patient, with typical Charcot Marie Tooth condition, had a significant worsening of the motor condition at the age of 37, evolving with significant weight loss, sexual dysfunction, frequent falls, and difficulty walking, requiring unilateral support. Genetic test revealed mutation in the PMP22 gene and a mutation in the gene that encodes TTR, Val142Ile.

Methods:
We describe a case of a man who presented a history of difficulty walking since he was 5 years old, with stumbling and frequent falls. The condition remained stable until 5 years ago, when he noticed a progressive worsening of gait, with muscle weakness and atrophy in the upper and lower limbs. In addition, the patient had signs of dysautonomia, such as erectile dysfunction, orthostatic intolerance, and palpitations.

Results:
Electroneuromyography revealed severe sensorimotor polyneuropathy. Genetic testing revealed two genetic mutations, PMP22 causing Charcot-Marie-Tooth disease and Val142Ile, a gene responsible for hereditary transthyretin amyloidosis.

Conclusions:
Charcot Marie Tooth disease is a hereditary disease that manifests in adolescence or early adulthood, with loss of sensitivity, weakness, deformity and muscle atrophy mainly in the lower limbs. Hereditary amyloidosis courses with progressive polyneuropathy, often associated with dysautonomia causing multisystem symptom. Genetic test indentified tte gene that causes hereditary amyloidosis, a potentially treatable disease. As the patient was still able to walk with bilateral support, patisiran was indicated. It is important to be aware to atypical signs of a disease looking for other diagnostic alternatives or even concomitant diseases as was this case

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: amyloidosis, charcot marie tooth, neuropathy, genetic

T2-Relaxometry: Identifying Imaging Biomarkers In A Large Cohort Of Symptomatic And Asymptomatic Hereditary Transthyretin Amyloidosis

Poster No:
P 085

Authors:
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Introduction:
Previously, the two magnetic resonance neurography (MRN) markers T2-relaxation time (T2app) and proton-spin-density (ρ) detected nerve injury in a small cohort of ATTRv amyloidosis. With this study we aim to develop new imaging biomarkers for monitoring the disease onset and progression by testing the reliability of MRN markers to quantify nerve lesions in a large cohort of symptomatic and asymptomatic ATTRv amyloidosis, and by performing extensive correlation analyses with demographic, clinical and electrophysiologic parameters.

Methods:
80 participants with either symptomatic ATTRv amyloidosis (N=40) or asymptomatic carrier status of the variant transthyretin gene (varTTR) (N=40) as well as 40 non-amyloidogenic controls prospectively underwent 3T MRN with T2-relaxometry sequences of the sciatic nerve. Subsequently, nerve T2app and ρ were calculated based on manually delineated regions of interest. Among other parameters, the neuropathy impairment score for the lower limbs (NIS-LL) was determined and extensive nerve conduction studies were performed.

Results:
ρ was highest in symptomatic ATTRv amyloidosis, decreased significantly in asymptomatic varTTR-carriers, and further decreased significantly in healthy controls. It was also slightly higher in severely affected ATTRv amyloidosis patients than in mild or moderately affected patients. T2app was significantly increased in symptomatic ATTRv amyloidosis only. While ρ showed excellent correlations with electrophysiologic parameters on a subclinical level in asymptomatic varTTR-carriers, T2app correlated well with the NIS-LL and electrophysiologic parameters in symptomatic ATTRv amyloidosis.

Conclusions:
ρ detects subclinical nerve lesions and separates clinically and electrophysiologically complete asymptomatic varTTR-carriers from symptomatic patients and controls while correlating well with electrophysiologic parameters. T2app strongly distinguishes symptomatic ATTRv amyloidosis from varTTR-carriers and controls, and correlates well with clinical and electrophysiologic markers in symptomatic ATTRv. Quantitative T2-relaxometry markers can assist in defining disease onset and conversion as reliable imaging biomarkers for an accurate disease and therapy-monitoring in the future while indicating different microstructural changes (demyelination versus axonopathy).

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: Research Grant from Alnylam Pharmaceuticals

Keywords: Hereditary transthyretin amyloidosis (ATTRv), Magnetic resonance neurography (MRN), T2-relaxometry, Polyneuropathy, Imaging biomarkers

Peripheral Nerve Involvement In Hereditary Spastic Paraplegia Characterized By Quantitative Magnetic Resonance Neurography

Poster No:
P 086

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Introduction:
Hereditary spastic paraplegias (HSP) are heterogeneous genetic disorders leading to progressive weakness and spasticity of the lower limbs, and are classified as either pure (e.g. spastic paraplegia (SPG) 4) or complex phenotypes (e.g. SPG7). Peripheral nerve involvement is frequent in SPG7, but controversial in SPG4. We aim to characterize lower extremity peripheral nerve involvement in SPG4 and SPG7 by quantitative magnetic resonance neurography (MRN) applying T2 relaxometry and magnetization transfer contrast (MTC) imaging.

Methods:
26 adult HSP patients carrying either the SPG4 or SPG7 mutation and 26 age-/sex-matched healthy controls prospectively underwent high-resolution MRN with coverage of the sciatic and tibial nerve from the proximal thigh to the tibiotalar joint. Dual-echo turbo-spin-echo sequences with spectral fat saturation were utilized for T2 relaxometry, measuring the quantitative microstructural markers T2 relaxation time and proton spin density, as well as for morphometric quantification. Two gradient echo sequences, one with and one without an off-resonance saturation rapid frequency pulse, were applied for MTC imaging and calculation of the magnetization transfer ratio (MTR). All HSP patients underwent detailed neurologic and electrophysiologic assessments.

Results:
All evaluated MRN markers (proton spin density, T2-relaxation time, magnetization transfer ratio (MTR), and cross-sectional area) were decreased in SPG4 and SPG7 indicating a chronic axonopathy. Proton spin density was superior in differentiating subgroups and in identifying subclinical nerve damage in SPG4 and SPG7 patients without polyneuropathy. Microstructural MRN markers correlated well with clinical symptom scores and electrophysiologic results.

Conclusions:
MRN characterizes peripheral nerve damage in SPG4 and SPG7 as a neuropathy with predominant axonal loss. All analyzed quantitative MRN markers were decreased and differentiated between healthy controls and the two HSP groups. Evidence of peripheral nerve involvement in all SPG4 and SPG7 patients, even without clinically manifest polyneuropathy, challenges the traditional view of the existence of HSPs with isolated pyramidal affection.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: Research Grant from Alnylam Pharmaceuticals and from the Medical Faculty of the University of Heidelberg

Keywords: Hereditary spastic paraplegia (HSP), Magnetic resonance neurography, T2-relaxometry, Magnetization Transfer Contrast Imaging, Imaging biomarkers

Early Detection of Peripheral Neuropathy in Hereditary Transthyretin Amyloidosis (EDONA): preliminary results

Poster No:
P 087

Authors:
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Introduction:
Evaluate the utility of novel diagnostic tools for early detection of peripheral neuropathy in individuals with hereditary transthyretin amyloidosis (ATTRv).

Methods:
Preliminary analysis of an ongoing prospective study at the University of Pennsylvania. Participants were classified into ATTRv without neuropathy (i.e., carrier), ATTRv with neuropathy (i.e., symptomatic), and healthy controls. Evaluations included serum Neurofilament Light Chain (sNFL), bedside Quantitative Sensory Testing (bQST), and density of Meissner corpuscles (MC) and sweat ducts via in-vivo reflectance confocal microscopy (RCM). Along with traditional neuropathy assessment tools (nerve conduction studies, neuropathy impairment scale, Norfolk QOL, neuropathy symptoms and change, timed vibration). We described variables using median [IQR] or percentages where appropriate. We compared groups using the Wilcoxon rank sum test (alpha level of 0.05).

Results:
Fourteen carriers (38.5% females, age 54.7 [50.6-63.3]), six symptomatic (3.8% females, age 67.3 [65.3-70.8)]), and six healthy controls (19.2% females, age 43.7 [39.6–66.6]) were included. sNFL levels in symptomatic were 28.6pg/mL [19.3-53.87] compared to carriers (12.57 [9.04-15.32]; p=0.01) and healthy controls (7.15 [6.59-14.81]; p=0.03). Median vibration time in hallux of 2.3 [0-6.7] seconds in symptomatic compared to carriers (9.95 [5.4-15.0]; p=0.03) and healthy controls (15.7 [13.7-19.5]; p=0.02). Touch pressure threshold by monofilament on hallux was 2.5 [2.0-5.0] in symptomatic compared to carriers (1.0 [0-1.0]; p=0.02) and healthy controls (0.5 [0-1.0]; p=0.02). MC density in arch was 3.0/mm2 [2.0-4.0] in symptomatic compared to carriers (6.0 [5.0-14.0]; p=0.01) and healthy controls (12.0 [10.0-12.0]; p<0.01); comparison between carriers and controls was non-significant for all these assessments. These findings were supported by significant differences in traditional neuropathy assessment tools in symptomatic vs carriers and controls.

Conclusions:
sNFL, bQST, and RCM may have utility for the detection of neuropathy in patients with ATTRv. Further data will be collected using a bigger, age- and matched-sample to better characterize group differences using these tools.

References:

No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Transthyretin Amyloidosis, Reflectance confocal microscopy, Neurofilament, Quantitative sensory testing

In-Vivo Reflectance Confocal Microscopy of Meissner Corpuscle Density in CMT1A: Data from the ACT-CMT Study

Poster No:
P 088

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Introduction:
Therapies under development for Charcot Marie Tooth Type 1A (CMT1A) require validated clinical trial endpoints. Accelerate Clinical Trials in Charcot-Marie-Tooth Disease (ACT-CMT) is an NIH-supported, multi-center, international clinical trial readiness study that aims to validate clinical outcomes and biomarkers for CMT1A. One aim focuses on in-vivo reflectance confocal microscopy (RCM) of Meissner corpuscle (MC) density, which has emerged as a promising candidate monitoring biomarker for sensory nerve involvement.

Methods:
Participants with CMT1A and healthy controls aged 18 to 75 were enrolled across multiple sites. Serial assessments over three years are ongoing and include in-vivo RCM of MC densities and tactile thresholds at the distal palmer surface of digit V (DV) and the thenar eminence (TE), CMT-Functional Outcome Measure (CMT-FOM), CMT Neuropathy Score (CMTNSv2-R) and Exam Score (CMTES-R), CMT-Health Index (CMT-HI), MRI of intramuscular fat fraction, and electrophysiology.

Results:
Baseline MC densities were quantified in 98 participants with CMT1A and 20 controls, with comparable gender and age distributions. In CMT, MC densities were measurable in all participants at TE and 98% of participants at DV, while radial sensory nerve action potentials were evocable in only 33% of participants. MC densities were lower in CMT than controls at DV ($p = 0.002$) but not at TE. MC densities were associated with tactile thresholds and clinical severity measures, including CMTNSv2-R, CMTES-R, CMT-FOM fine motor function, balance, and gross motor function subtests, and CMT-HI numbness and hand subscales. Six-month longitudinal data will be analyzed and presented.

Conclusions:
In-vivo RCM of MC density is a non-invasive objective measure of sensory nerve involvement in CMT1A that is associated with clinical severity measures on cross-section evaluation and is not limited by a floor effect. The ongoing longitudinal study will further evaluate the role of in-vivo RCM of MC density as a monitoring biomarker in CMT1A.

References:
No

References 1:

References 2:

References 3:

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Grant Support: Supported by NIH grant # NIH 1 U01 NS109403-03 to DNH.

Keywords: Charcot-Marie-Tooth, biomarker, Meissner corpuscle, reflectance confocal microscopy

A novel quantitative foot muscle fat fraction protocol reliably measures disease progression in Children and Young People with CMT1A over 12 months

Poster No:
P 089

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Introduction:
We have previously demonstrated that quantitative muscle fat fraction (FF) at calf level is a responsive biomarker over 12-months in CMT1A.(1,2) Subgroup analysis demonstrated that lower responsiveness was seen in those with baseline FF <10%, and that those patients were younger and had lower CMTES.(2) We sought to demonstrate whether distal measurements – of the foot, could be used as an outcome measure in this patient group.

Methods:
Twenty-two participants with CMT1A (age 6-20, mean 13.1, 45% male) and 14 age-matched controls (age 6-20, mean 14.5, 36% male) were recruited in London and Iowa (p=0.58). Baseline and follow-up assessments included MRC scoring, ONLS, CMTESv2, CMT-Peds, CMT-HI and quantitative muscle MRI of both calves and one foot. We devised a novel foot neuromuscular MRI protocol. Following pilot analyses, blinded manual segmentation was completed and quantitative MRI parameters were calculated and analysed at baseline and follow-up.

Results:
16/22 participants with CMT1A (mean 522, s.d.163, range 348-902 days), and 11/14 controls (mean 476, s.d.174, range 355-892 days) returned for follow up visits. Preliminary analysis of foot data showed that baseline coronal forefoot mean Dixon FF (presented as mean±s.d.) for controls is 3.57±1.42% with no significant annual change -0.88±0.67% (standardised to 365-day intervals). In patients with CMT1A mean baseline FF was 25.93±20.8% with annual increase 2.14±2.46%, p=0.001, standardised response mean (SRM) 0.87, confirming high responsiveness. Baseline foot FF in patients correlated with age ρ=0.59, p=0.008 (Regression analysis shown in Fig 1), and CMTES ρ=0.59 p=0.01.

Conclusions:

Baseline coronal FF at forefoot was higher in patients (25.9%) than controls (3.6%) and increased over 365 days by 2.14 in the patient group only, with high responsiveness. We have demonstrated that coronal foot FF is a viable outcome measure for clinical trials in children and young people who have CMT1A.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: The Muscular Dystrophy Association

Keywords: CMT, MRI, Biomarkers

Clinical and radiologic features of *SPG11* mutation-related hereditary spastic paraplegia

Poster No:
P 090

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Introduction:
Mutations in the SPG11 gene are responsible for complicated hereditary spastic paraplegia (HSP) characterized by the thinning of corpus callosum. The purpose of this study was to investigate the clinical and radiologic characteristics in patients with SPG11-related HSP.

Methods:
Eight HSP patients with the thinning of corpus callosum on the brain MRI were investigated. A detailed neurological examination, neuropsychologic tests, and electrodiagnostic studies, including nerve conduction study, electromyography, and evoked potential, were performed. Corpus callosum was divided into seven regions according to Witelson's guideline, and evaluated the location and pattern of the thinning.

Results:
Six patients, including two identical twins, were finally diagnosed with SPG11-related HSP. The median age at onset was 16.5 years (range, 13-38 years). Besides slowly progressive paraparesis, spastic dysarthria and urinary incontinence were common. All subjects, including three previously diagnosed with mental retardation, had a learning difficulty and calculation difficulty. Full-scale Intelligence quotient revealed a score between 42 and 72 on the Wechsler Adult Intelligence Scale test. Mini-mental state examination scored between 26 to 28, and only attention/calculation domain was abnormal. Ears-of-the lynx sign at the forceps minor and the thinning of rostral body in the corpus callosum were exclusively observed on the fluid-attenuated inversion recovery (FLAIR). Mild T2/FLAIR hyperintensity at the forceps major and the thinning of anterior midbody were also seen in four subjects. Leg motor evoked potential (MEP) tests were abnormal, while arm MEP abnormality was observed in three.

Conclusions:
Attention/calculation dysfunction were common in SPG11-related HSP. Leg MEP was absent, and arm MEP became abnormal with time. The body part of corpus callosum became thinned in common, especially significant in the rostral body.

References:
No

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References 2:

References 3:

References 4:

Grant Support:

Keywords: SPG11, Spastic paraparesis, Corpus callosum, Magnetic resonance imaging, Learning disability

Mechanisms of axonal degeneration and minigene therapeutic approach for Charcot-Marie-Tooth Disease Type 4B3

Poster No:
P 091

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Introduction:
Charcot-Marie-Tooth Disease type 4B3 (CMT4B3) is a clinically heterogenous, early-onset and often severe form of hereditary neuropathy. Symptoms of CMT4B3 vary from an isolated demyelinating neuropathy to a complex neurodevelopmental syndrome with axonal neuropathy, cranial nerve involvement, and intellectual disability. CMT4B3 is caused by mutations in Sbf1, leading to dysfunction of the pseudo-phosphatase Myotubularin-Related Protein 5 (MTMR5). MTMR5 is an important yet poorly understood regulator of endo-lysosomal trafficking, autophagy, and nervous system development. Gene replacement therapy would be appropriate for CMT4B3. However, Sbf1 cDNA is larger (5,679bp) than the capacity of adeno-associated viral vectors (~4,700 bp) and creation of successful therapeutics is limited by our poor understanding of CMT4B3 disease pathogenesis.

Methods:
To elucidate the mechanism of pathogenic Sbf1 mutations, we differentiated motor neurons from patient-derived iPSCs to perform expression studies of various MTMRs and assayed for axonal injury via ELISA. To circumvent the size challenge of Sbf1, we've designed several Sbf1 'minigenes' based on comparative protein family, cross-species, and cross-domain investigations and have performed in vitro validation studies.

Results:
In our motor neuron model, we found that release of NF-L, an axonal injury biomarker, is elevated. We also noted residual MTMR5 expression, indicating that truncated MTMR5 could produce a toxic gain-of-function. Additionally, MTMR2 expression was decreased in CMT4B3 neurons, unlike in MTMR5-/- mice. For minigenes, one candidate recapitulates proper MTMR5 subcellular distribution and co-precipitates with the endogenous and active binding partner of MTMR5, MTMR2.

Conclusions:
Our findings provide evidence that CMT4B3 is an axonal neuropathy and that minigene replacement strategy could be a viable therapeutic avenue. Ongoing studies include investigation of motor neuron endo-lysosomal trafficking and phosphoinositide metabolism and how defects may lead to axonal degeneration. These motor neuron studies will pave the way for an image-based cellular phenotypic screening platform for CMT4B3 and will inform further refinement of candidate minigenes.

References:
No

References 1:

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References 3:

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Grant Support: Hunter's CMT4B3 Research Foundation: GR019966

Keywords: CMT4B3, iPSCs, Gene Replacement, Axonal CMT, Gene Therapy

The Plasma Membrane Of Schwann Cell Precursors Is Disturbed In Charcot Marie Tooth 1A Patients

Poster No:
P 093

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Introduction:
Charcot-Marie-Tooth disease type 1A (CMT1A) is the most common inherited neuropathy of the peripheral nervous system caused by a duplication of the peripheral myelin protein 22 gene (PMP22). Myelination is disturbed in CMT1A patients, and increasing evidence points towards defects in the functioning of the Schwann cell plasma membrane. Here, we investigated how the plasma membrane of CMT1A Schwann cells is disturbed.

Methods:
Schwann cell precursors (SCPs) were generated from CMT1A patient-derived induced Pluripotent Stem Cells (iPSC) and their isogenic controls.

Results:
Giant plasma membrane vesicles (GPMVs) were generated, and spectral imaging with Laurdan and Di-4-ANEPPDHQ showed that the ordering in the membrane was significantly reduced in CMT1A SCPs. Moreover, lipid raft dynamic analysis on cholera toxin b labeled cells showed that the mean square displacement (measure for raft mobility) was significantly reduced in CMT1A SCPs. The fraction of immobile/mobile rafts was also shifted, and confirmed more confined movement of rafts in the membrane of CMT1A cells. We could visualize PMP22 in the plasma membrane at super resolution using STORM microscopy, and observed single proteins and also aggregates of PMP22 in CMT1A and control cells. In addition, we found that PMP22 and integrin receptors colocalize in these raft domains in both isogenic and CMT1A SCPs. Bulk RNA sequencing highlighted integrin signalling as one of the top dysregulated pathways in CMT1A SCPs. Surprisingly, when performing a 3D hydrogel contraction assay, we could only observe a lossy interaction of both CMT1A and isogenic SCPs with collagen. However, when cells were cultured in 2D on a basal lamina-like structure we found that CMT1A SCPs show significantly increased time to close a scratch wound compared to isogenic control cells, implicating reduced cell migration.

Conclusions:
To conclude, our findings indicate alterations in the biophysical properties of the plasma membrane in CMT1A Schwann cells, which may affect myelination processes.

References:
No

References 1:

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References 3:

References 4:

Grant Support: Fonds voor Wetenschappelijk Onderzoek Vlaanderen to TV (12Z2620N)

Keywords: CMT1A, induced Pluripotent Stem Cells, Schwann cell precursors, Plasma membrane, Lipid rafts

Examining the Effects of Loss of Sipa1l2 on CMT1A Phenotypes Using Mouse Models

Poster No:
P 094

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Introduction:
In 2019, a patient-only GWAS of Charcot-Marie-Tooth type 1A (CMT1A) patients identified an association between intronic variants in signal induced proliferation associated 1 like 2 (SIPA1L2) and the strength of foot dorsiflexion, which is frequently diminished in patients. Knockdown experiments in rat schwannoma cells used siRNA to target Sipa1l2 and demonstrated that decreasing SIPA1L2 caused a corresponding decrease in peripheral myelin protein 22 (PMP22) abundance (1). Because PMP22 overexpression due to a tandem duplication causes CMT1A, SIPA1L2 became an interesting potential target for intervention in CMT1A, but in vivo tests were needed to validate a disease modifying effect of Sipa1l2.

Methods:
We deleted 1,877bp in the first exon of Sipa1l2 using CRISPR in C57BL/6J mice and then crossed the C3-PMP22 mouse model of CMT1A into the Sipa1l2 -/- background. These mice, and control littermates, were subject to neuromuscular phenotyping, nerve conduction velocity recordings, histopathology, and gene expression analysis by RNASeq.

Results:
Neuromuscular phenotyping revealed no significant improvements in CMT1A-associated deficits in muscular endurance or nerve conduction velocity; however, nerve histology reveals that Sipa1l2 knockout causes an increase in myelin thickness in femoral nerve motor branches and a decrease in the number of totally demyelinated axons in the C3-PMP22 mice. Gene expression analysis implicates pathways such as cholesterol biosynthesis in CMT1A pathophysiology and shows that Sipa1l2 knockout produces a gene expression signature also associated with cholesterol biosynthesis. Interestingly, knockout of the first exon of Sipa1l2 seems to normalize CMT1A-associated gene expression signatures for all but the most strongly enriched pathways.

Conclusions:
These results suggest that targeting Sipa1l2 in the C3-PMP22 mouse model does not produce significant improvements in neuromuscular disease phenotypes but does affect disease relevant processes such as myelination and may also partially eliminate the gene expression signatures of disease.

References:
Yes

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Tao F, Beecham GW, Rebelo AP, et al. Variation in SIPA1L2 is correlated with phenotype modification in Charcot- Marie- Tooth disease type 1A. Ann Neurol. 2019;85(3):316-330. doi:10.1002/ana.25426

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References 3:

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Grant Support: This research is supported by NINDS R21NS116936 and R37NS054154 awards to Robert W. Burgess.

Keywords: Charcot-Marie-Tooth, Mouse models, Demyelinating neuropathy, Validation, SIPA1L2

Correlation between Neurosonographic Features and Clinical, Electrophysiological Parameters in Charcot-Marie-Tooth Disease Type 1A Patients

Poster No:
P 095

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Introduction:
The purpose of this study is to analyze the correlation between ultrasonographic findings and clinico-electrophysiological parameters of Charcot–Marie–Tooth disease type 1A (CMT1A) patients.

Methods:
A total of 90 CMT1A patients were enrolled. Nerve cross-sectional area (NCSA) was measured in the determined sites of the median, ulnar, and radial nerves with ultrasound. Electrophysiologic and clinical data such as CMT neuropathy score (CMTNS) and functional disability scale (FDS) were collected. The correlation between NCSA, clinical, and electrophysiologic findings was analyzed respectively.

Results:
The nerve size of the CMT1A patients was significantly larger than the those of controls at all measured sites. Clinically, CMTNS and ulnar NCSA at the forearm correlated positively ($r=0.403$, $p=0.002$). The correlation between NCSA and FDS was insignificant statistically. In electrodiagnostic test, median NCSA at the midarm negatively correlated with compound muscle action potential (CMAP) amplitudes of median nerve ($R=-0.46$, $p<0.05$). Also, median motor neve conduction velocities (NCV) of the forearm and upper arm segments showed negative correlation with the median NCSA at the midarm ($R=-0.365$ and -0.420, respectively, $p<0.05$). Ulnar NCSA at the midarm negatively correlated to ulnar CMAPs ($R=-0.283$, $p<0.05$), and ulnar motor NCV of the forearm and upper arm segments ($R=-0.297$ and -0.360, respectively, $p<0.05$).

Conclusions:
This study revealed significant correlation between ulnar nerve CSA at the forearm and the clinical parameter in CMT1A patients. Median and ulnar NCSA at the midarm reflect the electrophysiological status. Neurosonography may provide complimentary information of hereditary neuropathy for electrophysiological status of patients.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Charcot-Marie-Tooth disease, Ultrasonography, NCS, CMTNS

Compound muscle action potential duration ratio for differentiation between Charcot-Marie-Tooth disease and CIDP.

Poster No:
P 096

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Introduction:
To elucidate the utility of the proximal to distal compound muscle action potential (CMAP) duration ratio to distinguish between demyelinating Charcot-Marie-Tooth disease (CMT) and chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) compared with nerve ultrasound.

Methods:
Thirty-nine demyelinating CMT patients and 19 CIDP patients underwent nerve conduction studies (NCS) and nerve ultrasound. NCS parameters, including CMAP duration ratio calculated by dividing the value at the proximal site by that at the distal site and nerve cross-sectional area (CSA) measured by ultrasound, were compared between the two groups. The diagnostic sensitivity and specificity of each parameter were analyzed.

Results:
CMT patients had significantly longer distal latency, lower motor conduction velocity, lower p/d CMAP duration ratio, and higher nerve CSA than CIDP patients ($p < 0.05$). The area under the curve (AUC) value of the CMAP duration ratio exceeded 0.95 when CMT was considered 'positive,' and a cut-off value of 1.13 resulted in high diagnostic sensitivity and specificity (84.6 and 100 % for median nerve, 97.4 and 85.7 % for ulnar nerve, respectively), whereas the AUC value of nerve CSA ranged from 0.70 to 0.81.

Conclusions:
The CMAP duration ratio could effectively distinguish between demyelinating CMT and CIDP. Adding the CMAP duration ratio to a routine NCS may improve the accuracy of the diagnosis of demyelinating CMT.

References:
No

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References 2:

References 3:

References 4:

Grant Support:

Keywords: Charcot-Marie-Tooth disease, chronic inflammatory demyelinating polyneuropathy, nerve conduction study, peripheral nerve ultrasound, duration ratio

Early, Short-Term Macrophage Targeting As A Long-Lasting Treatment Option For Charcot-Marie-Tooth Type 1

Poster No:
P 097

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Introduction:
Therapeutic approaches are urgently needed to mitigate CMT1 neuropathies. We previously identified neuroinflammation as a potentially treatable disease amplifier in distinct CMT1 mouse models. As an initial pharmacological proof-of-principle study, long-term targeting of nerve macrophages with the orally applied CSF-1 receptor specific kinase (c-FMS) inhibitor PLX5622 led to a substantial alleviation of the neuropathy in distinct CMT1 mouse models. However, considering translational options, clinically relevant questions emerged regarding treatment onset, duration and termination.

Methods:
In the distinct treatment paradigms applied, P0het and Cx32-deficient mice received PLX5622 (300mg/kg) to deplete nerve macrophages, followed by longitudinal functional tests. Inflammation in femoral quadriceps nerves and denervation of neuromuscular junctions in distal muscles was characterized by immunohistochemistry, while electrophysiology and electron microscopy scored nerve function and structure, respectively.

Results:
Early-onset PLX5622 treatment (starting at 1 month of age), led to preserved motor function and structure in CMT1B mice. However, when we specifically investigated the effect of a late-onset treatment (starting at 6 months of age), we failed to mitigate histopathological and clinical features, despite a similar efficacy of macrophages targeting as in the early-onset treatment regime. Surprisingly, terminating early-onset PLX5622 treatment at six months was still sufficient to preserve motor function in CMT1B mice at 12 months of age although macrophages re-appeared in nerves after treatment termination. Extending these unexpected findings to another CMT1 model, late-onset treatment failed, while terminating early PLX5622 treatment succeeded in alleviating disease outcome in Cx32-deficient mice.

Conclusions:
Our observations display an unexpected, long-lasting and clinically highly relevant therapeutic effect of early, but not late, macrophage depletion. Therefore, we suggest that the potentially adverse, continuous macrophage targeting might be unnecessary for disease alleviation. Future studies are necessary to decipher the molecular mechanisms behind the long-lasting effect of early treatment as well as the lack of treatment effect after late onset macrophage targeting.

References:
Yes

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Ostertag et al., Presymptomatic macrophage targeting has a long-lasting therapeutic effect on treatment termination in a mouse model of Charcot-Marie-Tooth 1, (2022) Exp Neurol. doi: 10.1016/j.expneurol.2022.114195.

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References 3:

References 4:

Grant Support: This study was supported by the Elite Network of Bavaria “Translational Neuroscience” and Plexxikon Inc and has been published in the following article: Ostertag et al., Presymptomatic macrophage targeting has a long-lasting therapeutic effect on treatmen

Keywords: Inherited peripheral neuropathy, Neuroinflammation, Macrophage, Colony stimulating factor, Denervation

Reclassification Of Patients With Phenotypic Hereditary Neuropathy Without Genetic Confirmation.

Poster No:
P 098

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Introduction:
As new opportunities in diagnostics and treatments of neuropathies have arisen, the importance of finding the exact cause of each patients neuropathy has increased. Whole genome sequencing (WGS) costs are going down and is expected to speed up the process of diagnostic clarification. The primary objective of the study is to identify the diagnostic clarification rate using WGS in patients with phenotypic hereditary neuropathy. Secondary objectives are to identify clinical factors as well as blood biomarkers that can help classify assumed hereditary neuropathies and prevent misdiagnoses.

Methods:
In this retrospective observational cohort study, we used patient records and ICD-10 codes to identify patients 18-70 years old previously or currently followed at our neuromuscular center from 2016-2022 diagnosed with a clinical phenotypic hereditary neuropathy without a genetic cinfirmation. The patients are reassessed with physical examination, hereditary neuropathy WGS gene panel, blood biomarkers including serum neurofilament light chain (sNfl) levels, creatine kinase and cryoglobulin, nerve conduction study, questionnaires concerning autonomic dysfunction (COMPASS-31), pain (S-LANNS) and daily activities (R-ODS).

Results:
In total 66 patients were identified by diagnosis. 34 patients have been included so far. Mean inclusion age was 55.1±11.5 years. 58.8% were male. Age of onset was 33.2±15.6 years. 35% had a family history of neuropathy and 30% a history with suspected asymmetric debut. Physical examination showed a UENS score of 23.6±10.5 (mean±SD) and MRC-sum score of 55.9±3.3. Total weighted COMPASS-31 score was 12.3±7.7. 12 patients had pain, and four patients a S-LANNS score≥12. R-ODS score was 25.3±12.4. Creatine kinase mean levels was 230.2 U/L (min 55–max 1150). sNfl 20.1 ng/L (4.4-59.1). VEGF 70.6 ng/L (32–78). Cryoglobulins were detected in 7 of 11 preliminary tested samples. Molecular diagnoses and further results are pending.

Conclusions:
An update of the preliminary results will be reported at the upcoming annual PNS meeting.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Hereditary neuropathy, Whole genome sequencing, Cohort study, Biomarkers, Charcot-Marie-Tooth

Dosage Effects of PMP22 on Nonmyelinating Schwann Cells in Hereditary Neuropathy with Liability to Pressure Palsies

Poster No:
P 099

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Introduction:
Focal thickening of the myelin sheath, also known as tomacula, is a characteristic pathological feature of patients with hereditary neuropathy with liability to pressure palsies (HNPP). However, a deeper understanding of the pathology underlying unmyelinated fibers and nonmyelinating Schwann cells is required.

Methods:
Electron microscopic examination of sural nerve biopsy specimens was performed for 14 HNPP patients with peripheral myelin protein 22 (PMP22) deletion, and their results were compared to 12 normal controls and 14 Charcot-Marie-Tooth disease type 1A (CMT1A) patients with PMP22 duplication.

Results:
The number of unmyelinated axons in a single axon-containing nonmyelinating Schwann cell subunit in the HNPP group significantly increased compared with that in normal controls (1.99 ± 0.66 vs. 1.57 ± 0.52, $p < 0.05$). Conversely, these numbers significantly decreased in the CMT1A group compared with those in normal controls (1.16 ± 0.16, $p < 0.05$). Some unmyelinated axons in patients with HNPP were incompletely surrounded by the cytoplasm of Schwann cells, almost as if the Schwann cells failed to form mesaxons; such failure in mesaxon formation was not observed in normal controls or in patients with CMT1A.

Conclusions:
These findings suggest that PMP22 dosage affects nonmyelinating as well as myelinating Schwann cells.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: PMP22, hereditary neuropathy with liability to pressure palsies

A Genetic Analysis Of The Human Flavoproteome In UK Patients With Strachan's Syndrome

Poster No:
P 101

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Introduction:
Strachan's syndrome is comprised of a triad of sensory, optic and auditory neuropathy. It has long been accepted that the cause is nutritional deficiency of several B-vitamins however it bears a similar phenotype to other hereditary neuromuscular disorders such as Riboflavin Transporter deficiencies (RTD), formerly referred to as Brown-Vialetto-Van Laere syndrome (BVVLS) and Fazio-Londe disease. The biochemical profile is also similar to that seen in Multiple Acyl Coenzyme-A Dehydrogenase Deficiency (MADD). All of these conditions are caused by mutations in the flavoproteome, such as ETF and SLC52A2, and responsive to riboflavin. We have identified a group of Black British Caribbean individuals, including siblings, with a combination of painful sensory, optic and auditory neuropathy. In the majority, the neuropathy developed subacutely in the context of nutritional deficiency or systemic illness. Plasma acylcarnitine and urine organic acid profiles measured acutely revealed elevated short, medium and long chain acyl carnitines.

Methods:
The aim of this study was to perform gene analysis of the flavoproteome in a cohort of Black British Caribbean individuals, including 2 sets of unrelated siblings, with a clinical diagnosis of Strachan's syndrome.

Results:
Whole genome sequencing has been performed in a cohort of 13 out of 30 affected individuals. Gene analysis of approximately 90 genes encoding for flavin-dependent proteins, and therefore all dependent on riboflavin is in process, in order to better understand Strachan's syndrome and disorders of riboflavin metabolism.

Conclusions:
Strachan's disease is seen in Black Caribbean individuals most prominently during times of dietary restriction or acute illness. We propose that individuals with variants in genes which are riboflavin-dependent have a greater susceptibility to developing neuropathy. Early recognition and treatment with riboflavin may lead to improved outcomes.

References:
Yes

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Strachan H. On a form of multiple neuritis prevalent in the West Indies. Vol. 59, Practitioner. 1897. p. 477–84.

References 2:
Mosegaard S, Dipace G, Bross P, Carlsen J, Gregersen N, Olsen RKJ. Riboflavin Deficiency-Implications for General Human Health and Inborn Errors of Metabolism. Int J Mol Sci. 2020 May;21(11).

References 3:

References 4:

Grant Support:

Keywords: Strachan's syndrome, flavoproteome, riboflavin, whole genome sequencing

Addressing Diversity, Equity, Inclusion and Access within the Inherited Neuropathy Consortium

Poster No:
P 102

Authors:
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Introduction:
The Inherited Neuropathy Consortium (INC) Diversity Committee is working to improve delivery of clinical care to the true population of patients with inherited peripheral neuropathies through measures aimed at increasing representation of traditionally excluded populations among subjects enrolled in the INC and in the scientific workforce. Our committee is comprised of nine members including seven members from four INC sites in three countries who represent several disciplines and roles within the consortium and representatives from our patient advocacy groups.

Methods:
Current committee initiatives include (1) Trialing the use of updated and more descriptive race/ethnicity sub-categories that can be used in the United States, the United Kingdom, Italy and Australia; (2) Developing and validating CMT-specific virtual assessments into Spanish, Italian, Hindi, Farsi and Portuguese; (4) Providing resources for document translation and visit support to sites with staff who are bilingual and able to serve as centers for virtual enrollment and assessment of patients who prefer languages other than English; and (5) Development of the INC Diversity Intern position.

Results:
Our committee frequently collaborates with the Rare Disease Clinical Research Network (RDCRN) Diversity committee to share efforts and ideas across all RDCRN consortia. The INC's diversity committee served as a model for the formation of the RDCRN's committee. Two years after its formation, the RDCRN committee boasts a large membership, with 30-50 members joining the monthly calls, three subcommittees, a webinar series, and a workshop series. Several of our members are members of the RDCRN committee, and our committee chair is also a founding RDCRN diversity committee co-chair.

Conclusions:
Next steps for the INC diversity committee include additional initiatives aimed at addressing diversity among the INC workforce, development of marketing materials aimed at specific populations, and the creation of a patient liaison role.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: The Inherited Neuropathy Consortium is part of the NIH Rare Diseases Clinical Research Network (grant #1U54NS065712-01). The INC also receives funding from the Muscular Dystrophy Association and the Charcot-Marie-Tooth Association.

Keywords: Diversity, Workforce Development, Inclusion, Access

Integrin receptor profile disturbances in Charcot-Marie-Tooth disease type 1A Schwann cells

Poster No:
P 103

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Institutions:
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Introduction:
Charcot-Marie-tooth disease type 1A (CMT1A) is the most common inherited peripheral neuropathy, with motor and sensory dysfunction in the limbs and extremities as its main symptoms. A duplication of the PMP22-gene triggers CMT1A, resulting in altered Schwann cell differentiation and dysmyelination. Schwann cell differentiation and myelination depend on interactions with the endoneurium, effectuated mainly via integrin receptors located on the abaxonal cell membrane. The aim of this study was to determine integrin expression profiles, and the colocalization of integrin subunits in healthy and CMT1A Schwann cell models.

Methods:
To model CMT1A, we used C3-PMP22 mouse primary Schwann cells, CMT1A patient induced pluripotent stem cell-derived Schwann cell precursors (iPSC-SCPs) and PMP22-overexpressing human dental pulp stem cells (DPSCs). Immunocytochemistry was performed to determine presence of integrin α6, β1 and β4 in iPSC-SCPs and DPSCs, and integrin expression was assessed using qPCR on both mouse and human CMT1A cell models.

Results:
Integrin α6 and β1 levels are significantly decreased in CMT1A iPSC-SCPs compared to isogenic controls, but significantly increased in PMP22-overexpressing DPSCs. Additionally, CMT1A iPSC-SCPs display less integrin α6β1 heterodimer formation, in contrast with PMP22-overexpressing DPSCs, where an increased colocalization of integrin α6β1 is observed. Furthermore, CMT1A iPSC-SCPs have a lower expression of integrin α5, α6, α7 and β1 transcripts than isogenic controls, whereas PMP22-overexpressing DPSCs do not show significant alterations in their integrin transcriptomic profile. Interestingly, primary C3-PMP22-derived Schwann cells display an increase in integrin α6 and β1 mRNA levels, and an increasing trend in integrin β4 expression, whereas C3-PMP22 Schwann cells have a decreased integrin α6 expression.

Conclusions:
Overall, these results highlight a cell-type specific effect of PMP22-overexpression on the integrin profile in murine and human CMT1A models.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: CMTA - Charcot-Marie-Tooth association FWO - Fonds Wetenschappelijk Onderzoek BOF - Bijzonder onderzoeksfonds, UHasselt

Keywords: Integrin, Schwann cell, Charcot-Marie-Tooth disease type 1A, iPSC, peripheral nervous system

Novel Pathogenic Gene Variants in Thai Children with Inherited Peripheral Neuropathy

Poster No:
P 104

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Introduction:
Inherited peripheral neuropathy is a challenging disease to diagnosis and treat as it is caused by mutation in over 100 genes. It causes long-term disability and is a significant health care burden to society. We aim to investigate gene distribution and demonstrate the genotype-phenotype correlations with a focus on pediatric-onset disease.

Methods:
Next-generation sequencing and other analytical techniques were employed to identify pathogenic variants, including patients with positive duplication analysis of the PMP22 gene. Physical examination, electrophysiological studies, CMT Neuropathy Score (CMTNSv2), and CMT Pediatric Scale (CMTPedS)/CMT Infant Scale (CMTInfS) were performed in each patient.

Results:
Thirty-five patients with pediatric-onset inherited peripheral neuropathy were identified. Pathogenic variants were confirmed in 27/35 (77.1%) patients, including 10 novel pathogenic variants.

Conclusions:
The MFN2 gene accounted was the most common and the axonal type was predominant in these Thai patients with pediatric-onset inherited peripheral neuropathy.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: 1. Specific League Funds from Mahidol University (R016421009) 2. The Royal College of Pediatricians of Thailand

Keywords: Pediatric-onset, Inherited peripheral neuropathy, Charcot-Marie-Tooth disease, Genotype-phenotype correlations

A Novel SLC12A6 Mutation: The First Italian Report Of A Severe Early-Onset Intermediate Charcot-Marie-Tooth Phenotype

Poster No:
P 105

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Introduction:
Inherited peripheral neuropathies range from pure motor to pure sensory entities, with motor-sensory neuropathies (HSMN or Charcot-Marie-Tooth neuropathy) in between. The SLC12A6 gene encodes a K+-Cl− cotransporter (KCC3), pivotal in regulating neuronal excitability. Autosomal recessive homozygous or compound heterozygous loss of function mutations in SLC12A6 cause the HSMN with agenesis of the corpus callosum, while heterozygous mutations were reported in four patients with an early onset intermediate Charcot-Marie-Tooth (iCMT) phenotype.

Methods:
Herein, we report the first Italian patient showing a severe form of iCMT harboring a novel mutation in the SLC12A6 gene.

Results:
A 35-year-old man with unremarkable neurological familial history, referred to our neuromuscular center for evaluation of an early-onset motor-predominant neuropathy. During childhood, he complained of foot-dragging and underwent multiple surgeries for tendon retractions. In early adulthood, he presented a progressive distal motor and sensory impairment at the lower limbs which subsequently spread proximally and to the hands. Upon examination, at age 35, the cognition was normal, while dysmorphic face features were noticed. He had several contractures in the limbs and severe scoliosis. He complained of rhinolalia and dysphonia. He had severe weakness and muscle wasting in a distoproximal distribution. Impaired vibration and pinprick sensation was detected below the knees. Electrodiagnostic investigation was consistent with an iCMT neuropathy. Brain MRI was unremarkable. Respiratory evaluation detected a restrictive pattern and bilateral cord paralysis was documented with laryngoscopy. NGS analysis detected a previously unreported missense mutation (p.S674P) in the SLC12A6 gene, predicted as probably damaging by Polyphen-2 (0.998) and Mutation taster (Damaging,0) databases. His close family tested negative for the same mutation.

Conclusions:
Our patient showed an early-onset severe form of iCMT phenotype, along with vocal paralysis and restrictive respiratory pattern, these being unprecedented. SLC12A6 gene should be considered in the genetical work-up of patients showing an early onset intermediate severe CMT phenotype.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Charcot-Marie-Tooth, Neuropathy, Genetics, Inherited, HSMN

Characterization of De Novo Mutations in Korean Patients with Charcot-Marie-Tooth Disease

Poster No:
P 106

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Introduction:
De novo mutations (DNMs) which are not present in the parents are frequently observed in the rare genetic diseases including Charcot-Marie-Tooth disease (CMT). This study characterized genetic features of DNMs in Korean trio families with CMT.

Methods:
We investigated DNM cases from 416 trio families with CMT. The parental origins of DNMs were determined through haplotype analysis of SNPs flanking corresponding mutations. In addition, we also analyzed features of nucleotide sequences around mutation sites.

Results:
DNMs was identified in 102 trio families, thus, the incidence rate was determined to be 24.5% (CMT1A cases: 17.6%, other cases: 30.9%). The rates of DNMs were considerably variable according to genes. When we determined parental origins in 68 DNM cases (excluding CMT1A), paternal origin was significantly more frequent than maternal origin (84.4% vs. 15.6%). However, four DNMs in X-linked genes were all maternal origins. For the de novo CMT1A cases due to the unequal crossover, most DNMs were occurred between homologous chromosomes (86%), but four of five maternal originated cases were occurred between sister chromatids. For DNMs excluding CMT1A and indel cases, transition mutations were prevalent (86%), and 44% of mutations were occurred in the CpG sites.

Conclusions:
This study determined DNMs for the first time in large number of Korean trio families with CMT. As expected, most of the DNMs were determined to be paternal origin, but X-linked cases showed somewhat different pattern.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Charcot-Marie-Tooth disease, De novo mutation, Parental origin, Gender specificity, Korean

Atypical presentation of Charcot-Marie-Tooth disease type 2 by a mutation on the MME gene with electrophysiologic and ultrasound findings

Poster No:
P 107

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Introduction:
Membrane metalloendopeptidase gene (MME) mutation as the cause of axonal Charcot-Marie-Tooth disease (CMT) was reported in 2016. CMT2 caused by MME mutation inherited with autosomal recessive or dominant, and even sporadic patterns. MME-related CMT2 is usually characterized by late onset after age 30. Herein, we report a patient with CMT2 by MME mutation onset in young childhood.

Methods:
A 32-year-old male visited neurology clinic complaining of weakness and numbness in both lower limbs. His fetal development, delivery, and neonatal course were unremarkable. No other family members have similar symptoms. However, his leg motor milestones were delayed. He started to walk at 18 months, and he has not walked well since. He was diagnosed with sporadic CMT at age 10, but the genetic testing at that time did not find the causative gene. Weakness and numbness in the lower extremities and foot deformities slowly progressed. He got several foot surgeries until his late 20s. At age 27, he underwent genetic testing again with the next-generation sequencing panel, and MME mutation was detected. The neurologic examination revealed distal and lower limb dominant limb weakness (MRC grade 3). He could not detect a vibration sensation below the knee and second finger. Deep tendon reflexes were absent in the lower extremities and diminished in the upper extremities. A revised version of the CMT neuropathy score was 24 points.

Results:
Nerve conduction studies showed distal and lower limb dominant axonal type of sensorimotor polyneuropathy. Ultrasonography demonstrated decreased nerve cross-sectional area uniformly in all tested nerves of the upper and lower extremities and cervical nerve roots, except the sural nerves.

Conclusions:
This case demonstrates that the disease onset of CMT2 caused by mutations in the MME may occur at a younger age than previously reported and that ultrasound supplements the electrophysiologic findings.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Charcot-Marie-Tooth disease, MME gene, Ultrasonography

Initiative in The Study of Familial Amyloid Polyneuropathy in a Non-endemic Area

Poster No:
P 108

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Introduction:
The familial amyloid polyneuropathy (hATTR) has improved in its recognition due to the availability of genetic tests, a better education in rare diseases and new opportunities of treatments. Our objective was to report the identified cases in our country.

Methods:
We performed a multicentric, retrospective and descriptive study that included patients with pathogenic mutations.

Results:
We identified 138 patients, 75 males. Mean age 40 years old (range 16-78). Ninety-eight percentage were born in Argentina. The majority of them were living in Buenos Aires (78%) and the rest in other provinces. Val50Met was the more frequent mutation (77.5%) followed as Ala97Ser (5.79%), Try60Ala (4.34%), Val142Ile (3.62%), Ile127Val (2.17%), Try114Cys (0.72%), Ala36Pro (0.72%) and Glu62Asp (0.72%). Ninety patients had symptoms (46 had axonal neuropathy with gait disturbance after 50 years old and 44 had small fiber neuropathy before 50 years old). Others manifestations were: digestive 53 patients, genitourinary 40, cardiac 36, ocular 23, nephrological 13 and central nervous system 1. The latency between the onset of symptoms and the diagnosis was 1-10 years and the more frequent misdiagnosis were: cryptogenic axonal neuropathy (8), irritable bowel (5), CIDP (4), psychogenic disturbance (4), diabetic neuropathy (2), celiac disease (1), ALS (1), lumbar stenosis (1) and arthritis (1). Forty-three patients were asymptomatic, 50 patients were in stage 1, 28 patients in stage 2 and 9 patients in stage 3. Tafamidis, inotersen, patisiran, liver transplant, diflunisal and combination of doxycycline/tauroursodeoxycholic acid has been the treatment options for many of them. Fourteen patients died.

Conclusions:

The identified number of patients grew up in our country. Late onset presentations similar to non-endemic areas had a mild predominance and it was in concordance with the presence of non Val50Met variants. Misdiagnosis were important in neurology and recent treatments were offered to symptomatic patients.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: amyloidosis, val50met, late onset, transthyretin , mutations

A refractory cough for years ... Is it a CANVAS?

Poster No:
P 109

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Introduction:
Chronic-refractory-cough (CRC) is associated with a major degradation of quality of life and many patients suffer from the absence of a formal diagnosis explaining their cough. On the other hand, Ataxia-Cerebellar-Neuropathy-Areflexia-Vestibular Syndrome (CANVAS) is an autosomal recessive neurological disorder that appears in the sixth decade with sensory symptoms and/or ataxia. Interestingly, one of the first symptoms observed in these patients is a CRC, which can appear almost twenty years before the symptoms of neuropathy. In 2020, a biallelic intronic pentanucleotide expansion repeat in the RFC1 gene (ER-RFC1) has been identified in CANVAS patients. The objective of our study was to assess the proportion of CRC patients with ER-RFC1.

Methods:
We analyzed a cohort of 68 CRC patients. Chronic refractory cough was defined as chronic cough without cause or persistent cough with no improvement despite 12 weeks of inhaled corticosteroids. The gDNA, extracted from blood-total-EDTA, was analyzed by Long-Range-PCR and by Repeat-Prime-PCR.

Results:
Of the patients tested, 25% had at least one ER-RFC1, including 16.2% with ER-RFC1-bi-allelic, as observed in CANVAS patients. Interestingly, 8.8% of patients had a mono-allelic ER-RFC1. Patients with ER-RFC1 were statistically younger than non-ER-RFC1 group (44.6±12.4 vs 51.2±10.8, respectively, p=0.04). The proportion of patients whose triggers were dust/smoke or food was statistically higher in ER-RFC1-CRC patients. The presence of this genetic abnormality of RFC1 in CRC patients reinforces the idea of a neurogenic origin of this cough. A close follow-up of these patients will be performed from a neurological point of view.

Conclusions:
For the first time, we show that ER-RFC1 is present in 25% of patients with chronic refractory cough. We suggest to physicians who encounter CRC patients, for whom the different causes of cough will have been ruled out, to ask for an analysis of RFC1, in order to improve the diagnosis and the management of these patients.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: RFC1, CANVAS, Chronic refractory cough , Repeat expansion

Lysosomal Alterations In Charcot-Marie-Tooth Disease Type 1A

Poster No:
P 110

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Introduction:
Charcot-Marie-Marie Tooth disease type 1 (CMT1) is the most common hereditary demyelinating peripheral nerve disease, occurring in 1 in 2500 people worldwide. CMT1A is the most predominant subtype and is caused by a peripheral myelin protein 22 (PMP22) duplication. This aggregation-prone protein is mainly expressed by Schwann cells (SC). Previous research demonstrates that myelinating cells are in particular sensitive for lysosomal stress, making it presumable that PMP22 overexpression interferes with lysosomal function. Nevertheless, the role of lysosomes in CMT1A remains poorly understood. Here, we monitored lysosomal alterations in a CMT1A mice model and confirm our results in CMT1A patient-derived human induced pluripotent stem cell derived Schwann cell precursors (hiPSC-SCP).

Methods:
The lysosomal marker LAMP1 and lysosomal enzymes cathepsin D and B (CTD, CTB) were monitored in 4-week-old sciatic nerves and primary isolated SC. These results were further evaluated in CMT1A patient-derived hiPSC-SC compared to their isogenic controls.

Results:
In sciatic nerves, protein levels of LAMP1, CTD and CTB were significantly increased in C3 vs. WT mice, using western blot and immunostainings. Additionally, in primary SC LAMP1, CTD and CTB protein levels were visualized, showing a strong significant increase in CMT1A SC. In addition, CTB activity was significantly elevated in primary CMT1A SC. These data was confirmed in CMT1A patient-derived hiPSC-SCP, showing significantly higher LAMP1, CTD and CTB levels in CMT1A compared to their isogenic controls.

Conclusions:
We could demonstrate a significant increase in lysosomal numbers, lysosomal enzymes and their activity in the peripheral nerves of CMT1A mice and primary CMT1A Schwann cells. In addition, these data could be recapitulated in CMT1A patient iPSC-derived SC precursors. These results indicate significant changes in lysosomes and their enzymes in CMT1A disease. Nevertheless, further research is necessary to further explore the mechanism and consequences of these lysosomal changes, and their possible use as a therapeutic target.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: Belgium - Fonds wetenschappelijk onderzoek (FWO)

Keywords: CMT1A, Schwann cell, lysosomes, cathepsins

Axonal cytoskeleton alterations precede neurodegeneration in Transthyretin Amyloid Polyneuropathy

Poster No:
P 111

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Introduction:
Transthyretin Amyloid Polyneuropathy (ATTR-PN) is a neurodegenerative disease characterized by the deposition of aggregates of mutated transthyretin (TTR), particularly in the peripheral nervous system, resulting in a dying-back sensory axonopathy. Axonal degeneration has been associated with disruption of the neuronal cytoskeleton in several neuropathies. In this work we explored the role of cytoskeleton disruption in ATTR-PN pathogenesis.

Methods:
We used an ATTR-PN mouse model that carries the human TTRA97S mutation (hTTRA97S mice), and recapitulates the sensory neuropathy typical of the disease, to perform live-imaging of cytoskeleton dynamics in sensory axons.

Results:
We showed that dorsal root ganglia (DRG) neuronal cultures from hTTRA97S mice present disrupted actin organization in the growth cone and axonal actin alterations, in a process mediated by Rac1. Importantly, actin defects preceded in vitro axonal degeneration of hTTRA97S DRG neurons. Having seen a disruption in actin organization in the hTTRA97S mouse model, we were interested in detecting whether microtubules and/or axonal transport were also altered. Ex-vivo live imaging of sural nerves from hTTRA97S mice presented defects in axonal mitochondrial trafficking and in microtubule dynamics at an age preceding axonal loss in vivo.

Conclusions:
Overall, our data suggests a generalized dysfunction of the axonal cytoskeleton in peripheral neurons preceding neurodegeneration in an ATTR-PN mouse model. We now aim to further dissect the molecular mechanism mediating cytoskeleton damage and validate cytoskeleton alterations in human samples, both iPSCs-derived neurons and sural nerve biopsies, from ATTR-PN patients. This work will contribute to unravel novel mechanisms of axonal degeneration in ATTR-PN which might impact on novel therapeutic strategies for the disease.

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Yes

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Kan H-W, Chang H, Lin W-M, Yu I-S, Lin S-W, Hsieh S-T. Neuropathol Appl Neurobiol. 2018.

References 4:

Grant Support:

Keywords: transthyretin, axon, neuronal cytoskeleton, peripheral neuropathy, live-cell imaging

Sorbitol Reduction via AT-007 Prevents Synaptic Dysfunction and Neurodegeneration in Models of Sorbitol Dehydrogenase Deficiency

Poster No:
P 112

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Introduction:
Sorbitol dehydrogenase (SORD) deficiency has been identified as the most frequent autosomal recessive form of hereditary neuropathy, affecting roughly 10,000 patients worldwide. Loss of SORD causes high sorbitol levels in cells due to the inability to convert sorbitol to fructose in the two-step polyol pathway, leading to neurodegeneration. However, the underlying mechanisms of sorbitol-induced neurodegeneration have not been fully elucidated.

Methods:
A Drosophila model of SORD deficiency was characterized by locomotor behavior analyses, cellular characterizations, and high-resolution imaging. Reactive oxygen species (ROS) staining in the brain, ventral nerve cord, and muscle, as well as patient fibroblasts, was performed to understand the pathological changes at the molecular level. To reduce sorbitol accumulation by inhibiting conversion from glucose, a next-generation central nervous system (CNS) penetrant aldose reductase inhibitor (ARI) developed by Applied Therapeutics, Inc, named AT-007, was applied to patient fibroblasts, patient-derived motor neurons, and flies. Sorbitol levels in cells and fly brains were measured, and neurological phenotypes of flies were analyzed.

Results:
In a Drosophila model of SORD deficiency, we showed progressive synaptic degeneration in the brain, revealed by lamina vacuoles and electroretinogram abnormalities. In addition, with a novel automated behavior geotaxis monitoring system, we showed a locomotor impairment in SORD deficiency flies due to abnormal neuromuscular junction innervation. Finally, we found an accumulation of ROS in the CNS and muscle of the flies, as well as patient fibroblasts, indicating mitochondrial dysfunction. AT-007 significantly reduced sorbitol levels in patient fibroblasts, in patient-derived motor neurons, and in the Drosophila nervous system. Moreover, we demonstrated that feeding with AT-007 in Drosophila significantly improved locomotor activity, mitigated synaptic degeneration, and reduced ROS levels.

Conclusions:
Our findings establish the underlying disease pathogenesis and provide a potential treatment strategy for patients with SORD deficiency.

References:
Yes

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Grant Support:

Keywords: motor neuron, neuropathy, aldose reductase , Drosophila, reactive oxygen species

Impact of Baseline Polyneuropathy Severity on Vutrisiran Treatment Response in the Phase 3 HELIOS-A Study

Poster No:
P 113

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Introduction:
Hereditary transthyretin-mediated (hATTR) amyloidosis, also known as ATTRv amyloidosis, is a rapidly progressive, multisystem disease. Vutrisiran, an RNAi therapeutic, improved neuropathy and quality of life (QOL) versus external placebo in patients with hATTR amyloidosis with polyneuropathy in the Phase 3 HELIOS-A study (NCT03759379). This analysis evaluates the impact of baseline polyneuropathy severity on response to vutrisiran treatment.

Methods:
Patients were randomized (3:1) to vutrisiran (25 mg subcutaneous injection q3m) or patisiran (0.3 mg/kg intravenous infusion q3w), a reference group. The primary endpoint was change from baseline in modified Neuropathy Impairment Score+7 (mNIS+7) at 9 months versus an external placebo group from the APOLLO study (n=77). This post-hoc analysis divided patients into approximately equal quartiles of increasing baseline Neuropathy Impairment Score (NIS): Q1 ≥5.0─≤20.5; Q2 >20.5─≤44.1; Q3 >44.1─≤73.1; Q4 >73.1─≤127. Mean change from baseline to Month 18 was summarized by quartile for efficacy endpoints.

Results:
Across NIS quartiles, vutrisiran demonstrated benefit in mNIS+7 versus external placebo (mean change from baseline in mNIS+7 at Month 9/18: Q1, -3.3/-3.0 [vutrisiran] vs +13.8/+18.4 [external placebo]; Q2, -0.6/-3.1 vs +12.1/+24.5; Q3, -2.1/+6.2 vs +16.5/+33.1; Q4, +1.6/+3.2 vs +16.5/+30.7). Vutrisiran also demonstrated benefit versus external placebo across NIS quartiles for endpoints of QOL (Norfolk QOL-DN), disability (Rasch-built Overall Disability Scale), gait speed (10-meter walk test), and nutritional status (modified BMI). Overall, patients in lower NIS quartiles (less severe disease) at baseline maintained better scores at Month 18 compared with those in higher NIS quartiles. The external placebo group progressively worsened in all measures at Month 18.

Conclusions:
Vutrisiran demonstrated benefit in neurologic function and other key measures, versus external placebo, across all baseline polyneuropathy severities. Patients who initiated vutrisiran earlier in their disease course retained the highest level of neurologic function after 18 months, highlighting the importance of early diagnosis and treatment.

References:
No

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References 2:

References 3:

References 4:

Grant Support: Supported by Alnylam Pharmaceuticals

Keywords: hATTR amyloidosis, HELIOS-A, neuropathy, RNAi, vutrisiran

Drosophila Melanogaster As A Model For HINT1-Neuropathy

Poster No:
P 114

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Introduction:
Recessive loss-of-function variants in HINT1 cause a peculiar subtype of Charcot-Marie-Tooth disease: neuromyotonia and axonal neuropathy (NMAN). Although HINT1 is among the most common causes of recessive neuropathy, little is known about its functions in the peripheral nervous system. Several attempts to create HINT1-neuropathy animal models have been unsuccessful, making it increasingly difficult to answer the many open questions related to the disease. To address this gap, we established a HINT1-neuropathy Drosophila model.

Methods:
The CRISPR-Cas9 technology was used to knock out the Drosophila HINT1-orthologue (dHINT1). Additionally, a strain expressing the human wild type HINT1 (hHINT1) in this knock-out background was generated. These models were evaluated for the presence of neurodegenerative phenotypes. Developmental lethality was assessed by scoring the eclosion rate, followed by detailed characterization of neuromuscular junction (NMJ) morphology at the 3rd instar larval phase through immunohistochemistry and confocal microscopy. Finally, we assessed thermal nociception in the larvae.

Results:
qPCR demonstrated the absence of dHINT1 transcript in flies homozygous for the insertion and 50% of RNA levels in heterozygous animals as compared to wild type controls. Furthermore, expression of the neighboring genes, colt and CG15399, was unaltered. Homozygous loss of dHINT1 was not lethal. Knock-out larvae showed significantly reduced NMJ size and complexity. Moreover, they had increased response latencies to nociceptive thermal stimuli, indicating sensory impairment. Importantly, expression of hHINT1 rescued these abnormalities.

Conclusions:
Our dHINT1-knock-out larvae show signs of motor and sensory nerve impairment and neurodegeneration. The phenotypes can be rescued by expression of hHINT1 underscoring the functional homology between both orthologues. This model represents the first and so far, only complex multicellular system for studying HINT1-neuropathy. Moreover, our model may provide insight on the function of HINT1 in the peripheral nervous system in general. This knowledge could be translated into potential therapeutic targets for this severe disorder.

References:
No

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Grant Support: FWO 049217N FWO 11B3823N

Keywords: CMT, HINT1, Drosophila, Disease Mechanisms, Disease Modeling

Multidisclipinary care for Charcot-Marie-Tooth disease

Poster No:
P 115

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Introduction:
Charcot-Marie-Tooth (CMT) is an inherited neuromuscular disease. Clinical characterized by motor weakness and sensory impairment. However, patient may suffer from other symptoms such as pain, joint contracture, physical limitation and psychosocial issue. Multidisciplinary care is crucial for holistic supportive care for CMT patients resulted in improve quality of life. Multidisciplinary neuromuscular clinic is a one stop service that consist of several specialty healthcare providers who specialized in neurology, rehabilitation, physical therapy, nutrition, orthotic, Thai traditional medicine, special education, psychology and social worker. Multidisciplinary clinic reduced direct and indirect non-medical cost for family. The aim of the study is to demonstrate the satisfaction to multidisciplinary clinic by patients and caregivers as well as by health care providers

Methods:
This is a cross-sectional study. Satisfaction questionnaires were administered to caregivers and children with CMT who attend multidisciplinary neuromuscular clinic during November 2022 – May 2023. Patient received management in multidisciplinary neuromuscular clinic as the following orders. Patient was evaluated by neurologist, rehabilitation, physical therapist and follow by medical management, physical therapy and Thai traditional program. Then patient was assess and get the recommendation from nutritionist, special education teacher and social worker. Questionnaire for caregiver and children with CMT age > 7 years consists the data of advantage of the clinic, duration of service and follow up rate.

Results:
Total of 40 CMT children and caregivers were recruited. Over than 80% of caregivers satisfied to the multidisciplinary neuromuscular clinic. Advantage of this clinic is safe time, safe cost of transportation and personalize management suitable for individual patient. Over than 70% had good adherence to follow up visit.

Conclusions:
Multidisciplinary neuromuscular clinic is suitable for CMT patient by giving holistic care to individual patients. The advantage is safe time, safe cost of transportation and improve quality of life.

References:
No

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References 2:

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References 4:

Grant Support:

Keywords: Multidisciplinary care, CMT, Charcot-Marie-Tooth disease, one stop service, neuromuscular

Optical Genome Mapping Reliability And Accuracy In Detecting And Quantifying RFC1 Repeat Expansion in CANVAS

Poster No:
P 116

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Introduction:
Cerebellar Ataxia, Neuropathy, Vestibular Areflexia Syndrome (CANVAS) is a late-onset disorder typically associated with a biallelic intronic (AAGGG) repeat expansion in the RFC1 gene. Most patients show expansions longer than 1000 repeats. However, it has been shown that shorter expansions (i.e., 250 repeats) are disease-causing. Currently, Southern Blotting (SB) is the only technique able to accurately detect and estimate the size of large biallelic RFC1 expansions. However, it requires a large amount of DNA, is expensive and time-consuming. In this scenario, Optical Genome Mapping (OGM) represents a promising tool which allows the detection of large structural variations by labeling ultra-high molecular weight DNA molecules at specific sequence motifs. Therefore, the aim of this study was to explore the reliability and accuracy of OGM to detect and quantify RFC1 repeat expansions.

Methods:
A total of 10 CANVAS patients and 97 controls underwent OGM. SB was performed on the CANVAS samples. The size of RFC1 expansion estimated by SB and OGM was compared. Somatic instability was explored by the analysis of gaussian components in repeat- and non-repeat- containing DNA molecules of similar size.

Results:
OGM identified the biallelic repeat expansions > 250 repeats in all CANVAS patients but in none of the controls. OGM showed high concordance with the quantification of the repeat size by SB ($R = 0.96$). Further, it allowed to discriminate the presence of two expanded alleles in those cases in which SB had shown only one single homozygous expansion. No significant somatic instability of the repeat was found in the blood samples tested.

Conclusions:
OGM represents a promising tool for the genetic diagnosis of RFC1 in CANVAS, as well as other large repeat expansion disorders.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Optical Genome Mapping, CANVAS, RFC1, Repeat expansion, Somatic instability

Measuring ATTRv-neuropathy in real world practice: a proposed online protocol

Poster No:
P 117

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Introduction:
ATTRv-neuropathy is a progressive and fatal disease, but its natural history has been significantly impacted by an increasing number of drugs that act in different stages of the TTR amyloid formation. In this scenario it is important to identify for each drug who are the responders and the non-responders. This has obvious treatment implications.

Methods:
Based on the pivotal studies, we have established an informatized quantitative protocol to evaluate motor strength, sensation, dysautonomia and neurophysiology. Pain and tactile sensation were graduated considering 20 regions in the lower limbs, 16 in the upper limbs, 1 region at the abdomen, face and vertex. Each affected region scores 1. Vibration and postural sensations were graduated according to 6 regions (1st toe, ankle, knee, iliac crista, distal phalanx of digit II, wrist, and elbow). We additionally considered the visual analog scale for pain and presence of sensory ataxia. We also assessed postural hypotension, and 42 other autonomic manifestations. Strength was measured according to MRC scale considering 16 muscles in LL and 21 in UL. Neurophysiological indices: SNAP amplitudes of ulnar and sural; CMAP of peroneal and ulnar; SSR at the four limbs; and RR interval variation with deep breathing and Valsalva indices. Rather than a global sumscore of the individual parameters, we designed this tool to compare individually each of the individual items in sequential visits. This comparison can be displayed in graphic and table formats

Results:
The proposed on-line protocol is practical, objective and can bve easily used to follow the disease status of each patient

Conclusions:
We believe the proposed schedule is a sensitive and visual scale to identify clinically meaningful change from pre-symptomatic to symptomatic status and also to identify early responders vs non-responders for each specific treatment. It will certainly be a valuable instrument for those following patients with sensory, motor, and autonomic neuropathies.

References:
No

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References 2:

References 3:

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Grant Support:

Keywords: Amyloidosis, Neuropathy

A humanized yeast model reveals dominant-negative properties of neuropathy-associated alanyl-tRNA synthetase (*AARS1*) variants

Poster No:
P 118

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Introduction:
Aminoacyl-tRNA synthetases (ARSs) are essential enzymes that ligate amino acids to cognate tRNAs in the cytoplasm and mitochondria. Although ARSs are essential and ubiquitously expressed, loss-of-function (LOF) missense mutations in six dimeric ARS enzymes have been associated with dominant axonal peripheral neuropathy. This is a genetically and clinically heterogeneous inherited neuropathy characterized by the progressive loss of motor and sensory function in the distal extremities. Since all six implicated ARSs function as dimers and the majority of neuropathy-associated ARS variants cause a loss-of-function effect, we propose a dominant-negative pathogenic mechanism.

Methods:
To test for dominant-negative properties of neuropathy-associated ARS alleles, we developed a humanized yeast assay to co-express pathogenic human alanyl-tRNA synthetase (*AARS1*) variants with wild-type human *AARS1*. We then assessed for growth phenotypes in wild-type:wild-type and wild-type:mutant expressing yeast strains. We also biochemically tested for interactions between wild-type and mutant AARS1 proteins and engineered an *AARS1* mutation that reduces dimerization and tested it in *cis* to pathogenic mutations for reduced dominant growth phenotypes.

Results:
Here, we will present our currently unpublished data on a series of pathogenic, neuropathy-associated *AARS1* missense variants and show that pathogenic variants cause a loss-of-function effect and that they also repress yeast growth in the presence of the wild-type allele. Furthermore, we confirm that the wild-type and mutant proteins still interact to form dimers and show that reducing dimerization between mutant and wild-type AARS1 subunits rescues the dominant growth phenotype consistent with a dominant-negative effect.

Conclusions:
In sum, these data demonstrate that neuropathy-associated *AARS1* variants exert a dominant-negative effect, which supports a common, loss-of-function mechanism for ARS-mediated dominant peripheral neuropathy.

References:
No

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References 2:

References 3:

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Grant Support:

Keywords: tRNA synthetase, Charcot-Marie-Tooth disease, Genetics

Sensory-motor axonal neuropathy, optic atrophy, retinopathy, chronic intestinal pseudo-obstruction revealing a SLC5A6 homozygous mutation

Poster No:
P 119

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Introduction:
A 23 years old male presented with a sensory-motor neuropathy since early childhood, associated with optic atrophy, retinopathy, chronic intestinal pseudo-obstruction (CIP) and failure to thrive.

Methods:
He was born of consanguineous parents, one of his brother died at age 4, his two sisters were asymptomatic. He displayed distal muscular atrophy and deficiency in the four limbs with loss of ambulation at 20 yo, pes cavus, diffuse areflexia and distal hypoesthesia in the feet. There was no facial involvement. CIP was severe, having required a gastrostomy.

Results:
ENMG showed very low CPAM in the lower limbs and on the median nerves, sensory potentials were markedly decreased in all four limbs, whereas conduction velocities were within the range of normal, overall consistent with a sensory-motor axonal neuropathy. Brain MRI was normal, thymidine phosphorylase activity, peroxysomal explorations, amino acids chromatography were negative. Muscular biopsy did not show any mitochondrial defect, the respiratory chain was functionnal. Genetic screening for POLG, MFN2, OPA1 & 2, and more largely NGS for mitochondrial diseases were negative. There was no cardiac impairment, Forced Vital Capacity was 73%. Exome sequencing showed a homozygous variant in the SLC5A6 gene, for which each parents were heterozygous asymptomatic carriers. SLC5A6 is a sodium-dependent multivitamin transporter responsible for the transport of water-soluble vitamins biotin, panthonthenate and lipoate in both the disgestive system and across the blood-brain barrier. It has been previously reported in central and/or peripheral neurologic phenotypes, including failure to thrive, neuropathy, severe gasto-intestinal involvement ; thus is consistent with our patient's clinical picture.

Conclusions:
This diagnosis is of critical importance for the prognosis of the patient, as significany clinical improvement has been reported in SLC5A6 patients with supplementation in biotin, pantothenic acid and lipoate. Response to treatment will be a key element in validating this mutation in our patient.

References:
Yes

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Grant Support:

Keywords: Hereditary neuropathy, Vitamin, SLC5A5, Biotin, chronic intestinal pseudo-obstruction

A Case of Biallelic SORD Mutations Associated with Distal Weakness and Histological Signs of Myopathy

Poster No:
P 120

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Introduction:
Biallelic mutations in the sorbitol dehydrogenase (SORD) gene have been identified as a genetic cause of autosomal recessive axonal Charcot-Marie-Tooth disease 2 (CMT2) and distal hereditary motor neuropathy (dHMN). The most frequent pathogenetic variant is c.753delG (p.Ala253Glnfs*27) in homozygous or compound heterozygous state, which is responsible for about 10% of cases of undiagnosed CMT2 and dHMN. A case of juvenile amyotrophic lateral sclerosis associated with homozygous c.757delG mutation in SORD has recently been described, suggesting an expansion of the phenotypic spectrum of SORD diseases.

Methods:
We herein report a case of biallelic SORD mutations associated with histological signs of myopathy.

Results:
In 2013, a 16-year-old man was referred to our outpatient clinic for a slowly worsening gait disorder, which began at the age of 11. No other family members had similar complaints. Neurological examination revealed hypotrophy and weakness of the tibialis anterior and gastrocnemius muscles (Medical Research Council [MRC] score 4/5) and extensor hallucis longus weakness (MRC 4/5). Sensitivity and coordination were normal. The patient had reduced deep tendon reflexes, bilateral pes cavus, and mild steppage gait. Nerve conduction studies revealed low-amplitude compound muscle action potentials. Because of 1.5-fold increased CPK values and failure in identifying pathogenic variants in a Next-Generation Sequencing CMT-associated panel, gastrocnemius biopsy was performed with evidence of alterations suggestive of protein surplus distal myopathy. Finally, Whole-Exome Sequencing identified two pathogenic SORD variants in the heterozygous state: c.458C>A (p.Ala153Asp) (maternal origin) and c.757delG (p.Ala253Glnfs*27) (paternal origin).

Conclusions:
This is an isolated case report of compound heterozygosity for two SORD mutations associated with histological signs of myopathy, suggesting a further expansion of the phenotypic spectrum related to SORD mutations.

References:
Yes

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Cortese A, Zhu Y, Rebelo AP, et al. Biallelic mutations in SORD cause a common and potentially treatable hereditary neuropathy with implications for diabetes. Nat Genet. 2020;52(5):473-481.

References 2:
Bernard E, Pegat A, Vallet AE, et al. Juvenile amyotrophic lateral sclerosis associated with biallelic c.757delG mutation of sorbitol dehydrogenase gene. Amyotroph Lateral Scler Frontotemporal Degener. Published online 2021.

References 3:

References 4:

Grant Support:

Keywords: SORD, dHMN, distal myopathy

Development of a patient registry and natural history study to advance clinical trial readiness for TRPV4-related neuromuscular disease

Poster No:
P 121

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Introduction:
Dominant gain-of-function mutations of the calcium-permeable cation channel TRPV4 (transient receptor potential vanilloid 4) cause Charcot-Marie-Tooth disease type 2C and forms of distal spinal muscular atrophy, which share features of reduced strength in the upper and lower extremities and frequent vocal cord weakness. Fly and knock-in mouse models demonstrate that existing, orally-bioavailable small molecule TRPV4 antagonists are highly effective in ameliorating disease phenotypes. However, a clinical treatment trial for TRPV4 channelopathies will require improved understanding of the natural history and identification of relevant outcomes measures to assess therapeutic efficacy.

Methods:
To more fully define the clinical spectrum and natural history of TRPV4-related neuromuscular disease, we have developed a TRPV4 patient database, a TRPV4-specific medical history and symptom questionnaire, and initiated a multi-year TRPV4 natural history study.

Results:
Analysis of the 70+ patients in the patient registry demonstrates frequent weakness of proximal arm and leg muscles that is distinct from the pattern seen in patients with CMT1A. Pain and subjective sensory loss are infrequent, although sensory involvement is often detected clinically. Vocal cord weakness is common and can be quantified by laryngoscopy. Age of onset is bimodal, with peaks in the first two years of life and again in adulthood. In a majority of patients, disease progression is reported with respect to vocal cord dysfunction and proximal and distal upper extremity strength. Many patients also report various skeletal abnormalities, including scoliosis and arthrogryposis, among others. Ambulatory difficulties and vocal cord/respiratory difficulties are the most important disease manifestations as reported by patients.

Conclusions:
TRPV4 mutations cause an unusual and heterogenous motor-predominant phenotype with frequent vocal cord dysfunction, proximal weakness, gait difficulties, and skeletal abnormalities. These collective observations have informed development of a natural history study to define the clinical spectrum and evaluate specific clinical outcome measures and disease biomarkers that can be used in a future clinical trial.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: Muscular Dystrophy Association, MDA 964770 NIH/Inherited Neuropathies Consortium, S03663-01

Keywords: Charcot-Marie-Tooth disease, CMT2C, TRPV4, Natural history study, Treatment

Scaling-up a sustainable global credentialing system for CMT clinical trial evaluators

Poster No:
P 122

Authors:
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Institutions:
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Introduction:
There are significant challenges to conducting clinical trials in rare diseases such as CMT, including accurate natural history data and reliable clinical outcome assessments (COAs). Over the past decade, our program of research has collected extensive natural history data and developed reliable and sensitive COAs for CMT. However, a significant challenge remains, eradicating inaccurate measurement of COAs in clinical trials. The objective of this project is to create a global certification system for CMT clinical trial evaluators. The aims of this project are 1) expand our eHealth training and quality assurance platform to create a global network of rare disease stakeholders including advocacy groups, researchers, pharmaceutical sponsors and regulatory bodies, and 2) enhance the eHealth training resources to include reliability, benchmarking and automated monitoring of data collection across multiple sites.

Methods:
A process of consultation and co-design with the eHealth training development team will inform the expansion of the etraining and accreditation platform globally. The expanded system will include online reliability assessments and data monitoring using AI.

Results:
The eHealth training and quality assurance platform has successfully been used by the Inherited Neuropathy consortium to train clinical evaluators. With 705 registered users from 35 countries on www.ClinicalOutcomeMeasures.org, the expansion of the eHealth training and quality assurance platform to global clinical evaluators is essential to ensure reliability and accuracy in all data collected. This certification system can also be expanded across other neuromuscular diseases to promote clinical trial readiness for all rare neuromuscular diseases and accelerate initiation of clinical trials. The global adoption of the certification program will ensure appropriate education and training by all accredited clinical evaluators.

Conclusions:
This project will expand multi-site international clinical trial capacity by creating a certification standard to accredit a network of clinical evaluators and address the global problem of inaccurate assessment of COAs in clinical trials.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Clinical evaluators, Outcome measures, CMT, eHealth, Clinical trial

Validity of utilising different hand-held dynamometers for strength measures in the CMT-FOM and CMTPedS

Poster No:
P 123

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Introduction:
Muscle strength measures are important clinical outcome measures for individuals with neuromuscular disorders. The interchangeability of commonly used hand-held dynamometers in measuring the upper and lower limb isometric muscle strength is unknown. To expand the utility of existing normative reference values and facilitate reliable, comparable multisite data collection using clinical outcome assessments which involve muscle strength, the aim of this study is to compare hand-held dynamometers.

Methods:
Initially, each hand-held dynamometer was calibrated by determining its accuracy in measuring fixed known loads. Device interchangeability was determined using a standardised protocol by a trained, reliable clinical evaluator to assess shoulder external rotation, hip internal rotation and ankle dorsiflexion strength in 30 healthy participants using Citec, Nicholas, MicroFET2 and Commander hand-held dynamometers. Grip strength was measured using Citec, Jamar Plus and Baseline Hydraulic dynamometers.

Results:
Each device measured known loads accurately across their measurement ranges with minimal deviations. No measurement differences were recorded between Citec, Nicholas and MicroFET2 ($p>0.05$). Commander under-recorded hip internal rotation ($p<0.05$). Citec grip measures differed to Jamar Plus and Baseline Hydraulic ($p<0.01$). However, when controlling for grip diameter by comparing only participants using the smallest grip setting, all three dynamometers were interchangeable ($p=0.562$).

Conclusions:
Citec, Nicholas and MicroFET2 hand-held dynamometers are interchangeable for measuring upper and lower limb muscle strength. Existing normative reference values collected with these devices can be used interchangeably to accurately and precisely identify muscle weakness, monitor disease progression and evaluate treatment effect. For grip strength, all dynamometers were interchangeable if the smallest grip setting was selected.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Isometric muscle strength, Clinical outcome measures, Hand-held dynamometers, Interchangeability, Normative reference data

Elucidating CMT2E (p.N98S) pathomechanisms and attenuation via ASO therapy in iPSC-derived motor neurons.

Poster No:
P 124

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Introduction:
Missense variants in the neurofilament light chain gene (NEFL), an integral protein in the axonal cytoskeleton, cause Charcot-Marie-Tooth disease type 2E. Previous studies have established intracellular toxic NEFL-positive aggregates in motor neurons, but the precise molecular pathomechanisms have yet to be adequately described for CMT2E. NEFL is dynamically shifting between states of assembly and disassembly as the axonal cytoskeleton is continuously remodeled, a process driven by NEFL head domain phosphorylation. We hypothesize phosphorylation dysregulation of the NEFL head domain is the driver of NEFL misdistribution and NEFL-positive deposit formations observed in iPSC-derived CMT2E (p.N98S) motor neurons. Attenuation of this disease process via allele-specific antisense oligonucleotide (ASO) knockdown of mutant mRNA transcripts is key to preventing axonal injury.

Methods:
To understand changes in NEFL posttranslational phosphorylation modifications (PTM), we performed nano-liquid chromatography-mass spectrometry on precipitated NEFL from iPSC-derived motor neurons from healthy controls, isogenic control, and CMT2E (p.N98S) patients. To probe for consequential changes in binding partners associated with NEFL assembly/distribution, co-immunoprecipitation of NEFL, 14-3-3 and MYO5A was conducted using iPSC-derived motor neurons. Using 3D spinal spheroids derived from iPSC-motor neurons, co-localization, distribution, and anterograde/retrograde trafficking deficits of these known binding partners are being explored. The differential findings from these experiments are being assessed for attenuation of variant specific molecular phenotypes after ASO treatment.

Results:
This approach identifies key consequential PTM differences driving dysregulation of necessary binding partners associated with NEFL assembly and distribution, leading to NEFL-positive deposit formation. Treatment of iPSC-derived motor neurons with ASOs shows a clear attenuation of these variant specific molecular phenotypes.

Conclusions:
Our results suggest novel pathomechanistic findings and a viable genetic targeting strategy for a therapeutic application in this autosomal dominant disease. Optimizing this approach in patient derived pre-clinical iPSC studies is a key strategy under FDA rules to design early human trials.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Axonal neuropathy, ASO, gene therapy, axonal cytoskeleton, Neurofilament

Discovering the protein quality control at the outer mitochondrial membrane and its relevance in peripheral neuropathy

Poster No:
P 125

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Introduction:
Recent work from our lab has shown that the small heat shock proteins (HSPBs) execute an unexpected dual role in the mitochondrial protein quality control. We discovered that under basal condition, HSPBs are able to translocate into the mitochondrial inner membrane space (IMS) where they prevent protein aggregation. However, they immediately sequester at the outer mitochondrial membrane (OMM) under conditions of protein misfolding (induced by heat shock) or oxidative and mitochondrial stress (incited with hydrogen peroxide and CCCP respectively); but the reason still remains an enigma. Remarkable is that a Charcot-Marie-Tooth (CMT) causing Pro182Leu missense mutant of HSPB1 enriches on the OMM even under the basal condition; and the motor neurons derived from the Pro182Leu patient cell lines exhibit mitochondrial aberrations, including their dynamics, morphology and function.

Methods:
Using techniques such as Bimolecular fluorescence complementation system (BiFC), genome-wide CRISPR screening, and proteomics, we will systematically characterize the function of HSPBs at the OMM under normal and stressed conditions. Moreover, we will also study the interactomics and cytoprotective role of HSPBs (particularly at the OMM) in both naïve and knockout (KO) cell lines of HSPBs; which are particularly relevant under different cellular, stress, and peripheral neuropathy context.

Results:
HSPBs seem to be imperative for overall mitochondrial health and mitostasis, as their deletion leads to aberration in mitochondrial biology including dynamics, function and morphology. In addition to that, though HSPBs have been known to exhibit a cytoprotective role under stress, through our study we would be able to provide the detail mechanistic behind it.

Conclusions:
And lastly, HSPBs exhibit plethora of interacting partners in both cytosol and mitochondria, of which we emphasize on ERLINs due to its emerging importance in calcium biology and certain peripheral neuropathies such as, spastic paraplegia.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: FWO Fellowship (Fundamental Research), Belgium

Keywords: Mitochondria, small heat shock proteins (HSPBs), Oxidative stress, Mitochondria stress

Use of the 6-Minute Walk Test to detect fatigue in children with Charcot-Marie-Tooth diseases – a prospective study

Poster No:
P 126

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Introduction:
Charcot-Marie-Tooth (CMT) is an inherited peripheral neuropathy with many genetic and phenotypic variations. Fatigue is a common symptom across all patient subgroups contributing to short and long-term functional deterioration. The 6-minute-walk-test (6MWT) is an outcome measure used widely in paediatric neuromuscular disorders to assess performance fatigability. Our aim was to analyse percentage change between the first and the last minute of the 6MWT across CMT subtypes to establish whether performance fatigue worsens.

Methods:
In this prospective longitudinal study, we assessed 70 children (40 male, 30 female) with different types of CMT (40 CMT1A; 6 CMTX, 3 CMT4A; 2 CMT1B and CMT2A; and 17 other CMT subtypes). The mean age at baseline was 11.8 years (range 4.2 – 17.4). Forty-one children completed at least 1 year follow-up; 20 and 14 of them completed 2- and 3-years follow-up respectively.

Results:
Overall, there was -0.66% change (range -34% to 17%) between minute one and minute six of the 6MWT assessment. The CMT1A subgroup declined by -3.07% and CMTX declined by -1.17%. The biggest change was in the CMT4A (GDAP) and CMT1B (MPZ) subgroups with -9% and -7% respectively. However, both CMT2A (+3.5%) and DNM2 (+12%) showed an improvement. There was no statistical difference between different age groups or between sexes. Longitudinally, there was a minimal percentage change over the 3-year follow-up period with -0.29% in year one, +1.6% and +1.14% in years 2 and 3, respectively. Pain was present in 41% of the assessments conducted in this study but was not a confounding factor.

Conclusions:
The 6MWT has not previously been used to assess performance fatigue in children with CMT. Most patients did not demonstrate fatigue during the assessment, except for a few subgroups. We plan to further explore this data and present more detailed characteristics of this cohort of patients at this year's PNS conference.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: peripheral neuropathy, outcome measures , performance fatigue

Kennedy’s disease: A case series from India

Poster No:
P 127

Authors:
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Introduction:
Kennedy's disease (KD) is a rare X-linked lower motor neuron disease due to trinucleotide (CAG) repeat expansion in the first exon of the androgen receptor (AR) gene on Xq11-12. Only 2 genetically proven cases have been previously reported from India (43 and 49 CAG repeats). In this study, we aim to describe the largest series of genetically proven Kennedy's disease from India.

Methods:
All clinically suspected patients with Kennedy's disease were recruited prospectively in the MRC-funded International Centre for Genomic Medicine in Neuromuscular Diseases (ICGNMD) cohort. All patients underwent deep phenotyping, NCS, EMG, MRI Brain and Spine, Creatine Kinase, Fasting blood sugar, HbA1C, Lipid profile, LFT, TFT, FSH, LH, Testosterone and Estradiol. Genetic mutation confirmation was made by PCR using fluorescently labelled primers flanking the CAG repeat region of AR gene.

Results:
We suspected KD in 10 probands and relatives in the ICGNMD cohort. Genetic testing was positive in 4 probands and 2 affected relatives. One affected relative was not available for testing. Clinical features included facial weakness, facial fasciculations, tongue weakness, tongue fasciculations, hyporeflexia and gynecomastia. Mildly elevated CK and neurogenic changes in EMG were present in all. Two patients had sensory axonal neuropathy. ECG, MRI Brain and spine were normal in all. Three pateints had diabetes mellitus. All showed mild androgen resistance on hormonal evaluation. One proband and affected relative had hypothyroidism. There were mild dyslipidemia and elevation of AST and ALT (<100 U/L) in all patients. None had autonomic dysfunction, urinary obstruction or Brugada syndrome. PCR revealed following CAG repeats- Proband I: 46 (brother with gynecomastia alone- 19 repeats), Proband II: 47 (affected brother also 47 repeats), Proband III:47 (affected brother not tested yet), Proband IV: 48 repeats.

Conclusions:
We describe here the largest case series of Kennedy's disease from India with well characterized motor and non-motor features.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: Medical Research Council (UK) strategic award to establish an International Centre for Genomic Medicine in Neuromuscular Diseases (MR/S005021/1)

Keywords: Kennedy’s disease (KD) , Motor neuron disease, Spinal and bulbar muscular atrophy, trinucleotide repeat

Searching for commonalities among tRNA-synthetases-associated Charcot-Marie-Tooth neuropathies: Focus on the Integrated Stress Response

Poster No:
P 128

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Introduction:
Dominant mutations in seven aminoacyl-tRNA synthetases (aaRS) have been associated to Charcot-Marie-Tooth neuropathy (CMT), a progressive lifelong inherited disorder characterized by length-dependent axonal degeneration of motor and sensory peripheral nerves. These ubiquitously expressed enzymes catalyze the aminoacylation of tRNA by covalently linking specific amino acids to their cognate tRNAs. Interestingly, we and others demonstrated that some CMT-causing mutations do not abolish the aminoacylation activity, suggesting a neurotoxic gain of function mechanism. An attractive hypothesis is that a common signaling pathway is activated by the mutations in most if not all aaRS^{CMT}. Importantly, recent studies showed that YARS1^{CMT} and GARS1^{CMT} overexpression induced an integrated stress response (ISR)-mediated inhibition of protein translation in vivo. The ISR is a pro-survival homeostatic pathway activated in eukaryotic cells upon diverse stress stimuli (i.e. oxidative stress, amino acid deprivation, endoplasmic reticulum stress, etc.). In this project, we aimed to test whether ISR could be a common mechanism contributing to the aaRS^{CMT} pathology.

Methods:
We generated and characterized new fly models for four CMT-related aaRS (YARS1^{CMT}, GARS1^{CMT}, HARS1^{CMT}, AARS1^{CMT}) and compared them to the previously established ones for YARS1^{CMT} and GARS1^{CMT}. We then tested both up- and downregulation of the major ISR components in Drosophila using a retinal genetic modifier screen. Misexpression of the ISR key-players was confirmed by qPCR.

Results:
Our preliminary findings demonstrate both commonalities and differences in the effect upon modulation of key ISR molecular players on the rough eye phenotype specific for the aaRS^{CMT}-expressing flies.

Conclusions:
Our data require further validation using alternative, and preferentially neuron-specific, aaRS^{CMT} phenotypes (e.g. developmental lethality, neuromuscular junction morphology or locomotor performance). Our research will contribute to understanding the (common) pathomechanism(s) underlying the aaRS^{CMT} pathology and might suggest therapeutic strategies to alleviate this severe disorder.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Aminoacyl tRNA synthetase, Charcot-Marie-Tooth neuropathy, Disease modelling, Integrated stress response

Hereditary Transthyretin Related Amyloidosis: A Disease Hidden In Miscigenation In A Continental Country

Poster No:
P 129

Authors:
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Introduction:
Hereditary Transthyretin related Amyloidosis (ATTRh) is a rare multisystemic autossomic dominant disease whose identification across the world has been amplified in the last decade, as gene-related therapies were approved. The most common mutation, TTRpVal50Met, was initially described in caucasian and asiatic patients from endemic areas in Portugal, Sueden and Japan and the TTRpVal142 mutation was directly related to African-american descendants. The aim of the present study is characterize the distribution of ATTRh Brazilian population in the national territory and its ethnical aspects.

Methods:
This cohort study was descriptive, retrospective and enrolled a group of patients harboring suggestive phenotypes and at-risk family members of index cases with the TTR pathogenic mutation. It was conducted by three main Centers and recruited patients from other 16 centers. The local and national ethics committees in Brazil approved the study protocol.

Results:

From the 19 Brazilian Centers, distributed in the 5 brazilian regions, we enrolled a total of 784 patients with a TTR pathogenic mutation belonging to 261 families. 385 (49,1%) were male. The disease was manifest in 435 (55,5%) of patients and one third (33,3%) were asymptomatic carriers (11,2% unknown). The three most frequent TTR mutation were TTRpVal50Met (53,6%), TTRpVal142Ile (31,6%) and TTRIle127Val (8,4%). Other 13 mutations account for equal or less than 1% (Ala60Thr, Arg123His, Asp58Ala, Asp58Tyr, Glu109Lys, Glu112Lys, Ile88Leu, Phe64Ser, Phe84Leu, Pro44Ser, Pro791Ser, Thr80Ala, Val91Ala). The distribution by ethnicities showed that 378 (48,2%) patients identified themselves as white, 306 (39%) as mixed, 72 (9,2%) as black and 5 (0,6%) Asiatic (2,9% unknown).

Conclusions:
Our data shows that mutations in the TTR gene are highly prevalent in Brazil and that genetic heterogeneity is present, although 3 mutations clearly predominate, including the Val50Met, the Val142Ile and the Ile127Val, reflecting the Brazilian ethnicity. Genetic testing is mandatory in Brazilian patients that manifest compatible manifestations.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: Partially funded by Pfizer

Keywords: Amyloidosis, Transthyretin, Epidemiology, Brazil, Brazilian

Childhood Charcot-Marie-Tooth Disease Type 1A: Clinical Presentation And Disease Progression In A Large Italian Cohort

Poster No:
P 130

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Institutions:
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Introduction:
Charcot–Marie–Tooth disease type 1A (CMT1A) is the commonest hereditary neuropathy. This study aims to provide an in-depth longitudinal clinical characterization of a large pediatric cohort of CMT1A patients.

Methods:
Clinical evaluation of 124 CMT1A patients from 106 families was assessed using standardized scales (CMTPedS, CMTES). Follow-up range was 1-5 years (mean 4.5+3.2 years). Intrafamilial variability was studied by comparing 18 pairs of affected siblings, including 2 identical twins.

Results:
A positive familial history for CMT1A was present in 73% of patients; in 14.5%, diagnosis in relatives was obtained after the positive genetic result in the proband; 12.5% of cases were caused by a de novo CMT1A duplication. First signs of the disease were reported before the age of 6 years: gait disturbances (86.2%), foot deformities (33.8%). Patients came to the first neurological evaluation at a mean age of 8.5 years; main clinical signs were lower limbs (LL) areflexia (73%), foot dorsiflexion weakness (67%) and foot deformities (60%). Disease progression was observed in all patients and involved predominantly LL, including: proximal weakness (40%) and tendon retractions (52%), hand weakness (66%) and tremor (33%), scoliosis (22.5%). Sensory disturbances were present in many cases: paresthesia (38.7%), loss of superficial/deep sensation (44.5%), pain (11.2%). 50% of patients required orthotic devices and 14.5% underwent foot surgery by the age of 9 years. CMTPedS score worsened over a mean follow-up of 3± 0.9 years in the majority of patients. Significant variability was present in all siblings's pairs, both for age of symptoms onset and disease severity, and became more evident as age increased.

Conclusions:
The study confirms the usefulness of standardized scales as outcome measures for pediatric CMT1A, and provides data on the most relevant features of the disease and its progression, that must be considered when planning therapeutic strategies to improve patient's quality of life

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Charcot-Marie-Tooth disease , CHILDHOOD, progression, variability

Programmed axon death: moving from animal models into human disease

Poster No:
P 131

Authors:
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Introduction:
Programmed axon death is a widespread and completely preventable mechanism in injury and disease. Mouse and Drosophila studies define a molecular pathway involving activation of SARM1 NADase and its prevention by NAD synthesising enzyme NMNAT2. Animal models caused by genetic mutation, toxins, viruses or metabolic defects can be alleviated by blocking programmed axon death, for example models of CMT1B, chemotherapy-induced peripheral neuropathy (CIPN), rabies and diabetic peripheral neuropathy (DPN). The perinatal lethality of NMNAT2 null mice is completely rescued, restoring a normal, healthy lifespan.

Methods:
Animal models lack the genetic and environmental diversity present in human populations and this is problematic for modelling gene-environment combinations, for example in CIPN and DPN, and identifying rare, pathogenic mutations. We tested human gene variants in WGS datasets for loss- and gain-of-function variants in SARM1. To search for further rare disease variants in NMNAT2 and SARM1, we screened the rare disease component of the 100,000 Genomes, containing 35,422 rare disease families, including 786 participants with PNS motor and sensory disorders. We also screened the Queen Square dataset, including WES of 7,000 rare neurological disorder families. Novel, potentially pathogenic variants were also checked using GeneMatcher. In parallel, we are testing the hypothesis that function-altering NMNAT2 and SARM1 variants influence risk of CIPN and DPN using the Peripheral Neuropathy Research Registry and UK Biobank cohorts.

Results:
By testing human gene variants in WGS datasets, we identified enrichment of rare SARM1 gain-of-function variants in sporadic ALS, despite previous negative findings in SOD1 transgenic mice. Novel, potentially pathogenic variants have also been identified using GeneMatcher. We will report initial findings of different analyses.

Conclusions:
We aim to establish further collaborations to extend this research in multiple PNS disorders, using WGS and exome sequencing and functional testing of potentially pathogenic alleles.

References:
Yes

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References 2:

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Grant Support: Wellcome Trust grant : 220906/Z/20/Z

Keywords: Programmed axon death , axonal Neuropathy

Schmidt-Lanterman Incisure and Adherens Junction Defects in CMT1A and HNPP Myelin

Poster No:
P 132

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Introduction:
Increased and decreased dosage of the Peripheral Myelin Protein 22 (PMP22) gene cause dysmyelinating peripheral neuropathy, indicating that precise PMP22 expression is required for normal myelination. PMP22 duplication causes Charcot-Marie-Tooth Disease Type 1A (CMT1A) and PMP22 deletion causes Hereditary Neuropathy with Liability to Pressure Palsies (HNPP). CMT1A and HNPP are the most common inherited peripheral neuropathies, so it is remarkable how little we know about the physiological function of PMP22 and how underexpression and overexpression of this gene disrupts myelin integrity.

Methods:
To address these gaps, we are using CMT1A and HNPP mouse models. PMP22 is a member of the Claudin superfamily of proteins and current evidence suggests that PMP22 plays an undefined role in cell adhesion. Therefore, we characterized adhesion junction defects by performing confocal immunofluorescence imaging of teased tibial nerve fibers from these mice.

Results:
Results reveal normal tight junctions but dramatically altered adherens junctions (AJs) in CMT1A myelin as compared to wildtype. AJs are prominently localized to Schmidt-Lanterman incisures (SLIs), the cytoplasmic channels running through layers of compact myelin. E-Cadherin distribution is more punctate and the funnel shape structure of SLIs is often disrupted. The E-Cadherin defects correlate with changes in the AJ components β-Catenin and p120-Catenin and the gap junction component Cx29 at SLIs. Additionally, the distance between SLIs is decreased in CMT1A nerve fibers as compared to wildtype.

Conclusions:
Our findings demonstrate that AJs and SLIs are altered in CMT1A myelin. AJs are dynamic adhesion junctions that maintain tissue architecture. Our results suggest that AJs play a critical role in establishing SLI morphology, a process that is disrupted in CMT1A. This likely results in abnormal axo-glial communication and the increased SLI density in CMT1A likely reflects a higher metabolic need for these axons. Studies correlating AJ and SLI defects to disease severity and with HNPP myelin are ongoing.

References:
No

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References 2:

References 3:

References 4:

Grant Support: NIH NINDS K22 Career Transition Award (1K22NS125057)

Keywords: PMP22, Schwann cell, Myelin

Autosomal-recessive Charcot-Marie-Tooth Disease In Two Portuguese Patients With A Rare MME Mutation

Poster No:
P 133

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Introduction:
Charcot–Marie–Tooth disease (CMT) is caused by mutations in several genes and the clinical phenotype may be varied in accordance. MME mutations have been associated with an axonal form of CMT. We describe two Portuguese CMT cases with the same MME pathogenic variant.

Methods:
Review of the clinical records. Genetic testing was performed by next-generation sequencing.

Results:
Both patients presented at age 34 and 35 with lower limb weakness with distal-proximal progression over time. They were both from the Portuguese village of Santa Maria da Feira. The neurophysiological study confirmed a motor predominant polyneuropathy. Other causes were excluded. A genetic panel for hereditary polyneuropathies revealed the homozygous variant c.467del p. (Pro156Leufs*14) in the MME gene in both patients.

Conclusions:
This form of CMT should be included in the differential diagnosis of distal hereditary motor neuronopathy and even atypically symmetrical cases of amyotrophic lateral sclerosis (ALS).

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Charcot-Marie-Tooth

Large Scale Use Of HIPSC And Precision Medicine Approaches To Investigate CMT1A Severity

Poster No:
P 134

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Introduction:
There is significant unexplained variability in CMT1A severity, despite all CMT1A patients sharing a roughly equivalent 1.4 MB duplication on chromosome 17. Promising efforts by colleagues are underway to uncover novel genetic factors outside the duplicated region that may mediate severity. To complement these investigations, we believe that data from patient-specific human induced pluripotent stem cell (hIPSC)-derived Schwann cells offer a unique glimpse into CMT1A pathogenesis and can offer data on Schwann cell intrinsic factors potentially mediating CMT1A severity.

Methods:
Through the Johns Hopkins Precision Medicine Initiative, we are generating 20 hIPSC lines from 20 patients with mild CMT1A (6 patients), severe CMT1A (6 patients), typical HNPP (4 patients), and unaffected healthy controls (4 patients). Peripheral blood mononuclear cells from these 20 patients are being reprogrammed into hIPSCs using the NYSCF Global Stem Cell Array, which has shown increased reproducibility relative to conventional reprogramming techniques and has been validated as a platform for modeling complex genetic diseases on a population level. Patient-specific myelinating peripheral nerve organoids will be generating using the groundbreaking protocol developed by Van Lent, et al, and single cell transcriptomics, proteomics, and lipidomics will be used to identify potentially novel pathways mediating CMT1A severity and pathogenesis.

Results:
Patient enrollment is expected to be completed in Spring 2023, and hIPSC reprogramming and multi-omics analysis is anticipated to take 2-3 years to complete.

Conclusions:
We anticipate that this novel approach using patient-specific cellular reprogramming technologies may serve as a liquid biopsy in lieu of a primary Schwann cell biopsy and reveal unique insights into CMT1A and HNPP.

References:
Yes

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References 3:
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References 4:
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Grant Support:

Keywords: CMT1A, HNPP, Schwann cells, IPSC, Precision Medicine

Timing the Schwann Cell Injury Response in Relation to Axon Degeneration in Mouse and Zebrafish

Poster No:
P 135

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Introduction:
After peripheral nervous system (PNS) injury, axons degenerate in a process termed Wallerian degeneration, and Schwann cells adopt a repair phenotype. Wallerian degeneration is regulated by a cell intrinsic programmed axonal death pathway, with Sterile-α and Toll/interleukin 1 receptor motif containing protein 1 (SARM1) as a central activator. The interaction of the Schwann cell injury response and this axon death pathway is, however, incompletely understood and early injury responses have not been fully characterized spatially and temporally.

Methods:
We injured at the sciatic notch in wild-type and Sarm1 knockout mice, and performed bulk RNA sequencing of distal tibial nerves, at early timepoints prior to axon degeneration. We also investigated the timing of axon degeneration in unmyelinated axons in wild-type and Sarm1 knockout mice. Additionally, we live imaged a larval zebrafish model of PNS injury using 2-photon axotomy of the posterior lateral line nerve (PLLn), and investigated Schwann cell injury gene expression profiles, using third generation in situ hybridization chain reaction.

Results:
There are substantial gene expression changes in wild-type distal tibial nerves, remote from the injury site, at time points prior to significant myelinated axon degeneration. These gene expression changes did not occur at corresponding timepoints in Sarm1 knockout distal tibial nerves. We further show that while these gene expression changes occur prior to degeneration of myelinated axons, they coincide with the degeneration of unmyelinated axons. We demonstrate that in the PLLn 2-photon laser axotomy model in larval zebrafish, individual axons in the PLLn nerve degenerate at defined timepoints based on distance relative to the site of axotomy.

Conclusions:
This study demonstrates that unmyelinated axons degenerate faster than myelinated axons after traumatic nerve injury and supports a model of SARM1-dependent axon injury signaling to Schwann cells.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Schwann cell, Wallerian Degeneration, Sarm1, PNS Injury

A relatively common cause of hereditary motor neuropathy due to a founder mutation in VWA1

Poster No:
P 136

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Introduction:
Recently, rare biallelic variants in VWA1 encoding Von Willebrand factor A domain containing 1 were identified as a cause of a subtype of hereditary axonal motor neuropathy. The allele frequency of the most common pathogenic VWA1 variant p.(G25Rfs*74) is estimated to be around 1/1000 in European populations. Since its first description in early 2021, 34 patients from 23 families, including 17 patients from the UK or western Europe, have been reported in the literature.

Methods:
We present the clinical features and variants of 10 newly diagnosed patients from European-, and non-European ancestries along with reviewing all the previously reported patients.

Results:
Age of onset varied from congenital to adulthood. Disease progression was slow, and ambulation largely preserved. Clinical presentation included foot deformities, proximal and distal muscle weakness predominantly of the lower limbs, flexion contractures and spine deformities. Early axial weakness was observed in two patients and upper motor neuron signs in two further cases. Rarely sensory involvement, hypermobility and hyperlaxity, scapular winging, and tongue fasciculations were also reported. In some cases, myopathic changes were seen in the muscle biopsy and muscle imaging. Two patients had abnormal brain MRI with white matter abnormalities, and one patient presented with dysmorphic features. Misdiagnosis included Charcot-Marie-Tooth disease, spinal muscular atrophy, limb-girdle muscular dystrophy and facioscapulohumeral muscular dystrophy.

Conclusions:
Biallelic variants in VWA1 may be responsible for up to 1% of hereditary motor neuropathy cases in the European population. Therefore, early molecular testing for VWA1 variants needs to be considered in patients with unexplained hereditary motor neuropathy. With the expected increase in newly diagnosed cases of VWA1-related neuropathy in the coming years, a foundation will be established to raise public awareness and support clinical collaboration and research in this field, not only in the UK but also internationally.

References:
Yes

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Grant Support: MR/S01165X/1/Medical Research Council Centre for Medical Mycology MR/S005021/1/Medical Research Council Centre for Medical Mycology G0601943/Medical Research Council Centre for Medical Mycology

Keywords: Hereditary motor neuropathy, Neuromyopathy, VWA1, Genetics, Whole-genome sequencing

Clinical Trials in Charcot-Marie-Tooth Disease Support the Emergence of Therapeutic Trials Beyond Palliative Approaches

Poster No:
P 137

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Introduction:
The number of known causal CMT genes has accelerated through advent of next generation sequencing. The molecular therapeutic success in SMA, TTR, and Fabry provides hope for therapeutics in CMT. The objective of this study is to analyze the current environment of clinical trials in CMT.

Methods:
ClinicalTrials.gov was searched for interventional trials. All active studies were recalled June 2022. Excluded were suspended, withdrawn, or terminated studies.

Results:
A total of 287 active interventional CMT trials were identified. Of these, 246 (86%) were therapeutic trials including: procedural (n=125; wrist/elbow surgery, 21%; shock wave therapy, 11%; nerve hydrodissection, 11%), investigational drugs (n=57; 23%), devices (n=36; 15%), and physical therapy (n=28; 11%). Of all therapeutic trials, 77 were designated with a specific phase: phase 1-2 (n=33; 49%), phase 3-4 (n=34; 51%). The remaining 41 (14%) trials studied diagnostic testing (3%), functional outcomes (4%), natural history (4%), standard of care (3%). Academic setting occurred in 91%, pharmaceutical in 9%. Of the pharmaceutical and academic studies, 44% and 27%, respectively, were randomized, double-blinded, and controlled. Of all studies, 103 (36%) resulted in publications. Recent phase I pharmaceutical studies are specifically focusing on the safety of small molecule therapies (n=8) and AAV/nonviral gene therapy (n=3) in treating neuropathy.

Conclusions:
A majority of recent CMT trials are exploring procedural and molecular therapeutic options with significant participation of the pharmaceutical industry. Procedural based therapies ranged from testing drugs during procedures to comparing imaging modalities during procedures, but most were focused on studying surgical approaches. From these results, the current landscape of clinical CMT trials seems centered on identifying therapeutic surgical procedures that improve patient conditions beyond palliative care. These results suggest further need for biological therapeutic engagement from both academic and pharmaceutical companies.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: CMT, neuropathy, clinical trials

Charcot-Marie-Tooth disease: Genetic heterogeneity in a large Indian cohort

Poster No:
P 138

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Introduction:
Numerous genes cause distinct phenotypes in CMT. No major reports on Indian patients.

Methods:
To describe the clinical and genetic findings of CMT from a quaternary neurological center. A retrospective study of 110 CMT cases seen between 2006 and 2022 and confirmed by Next generation sequencing.

Results:
Mean ages at onset, presentation and illness duration in years are 16.7 ±15.4(1- 58.5), 24.0±15.8(1-63), 7.98±9.37(3 months-50 years). Consanguinity= 32(29%). M:F=1.6:1. Most common variants:GDAP1[13(homozygous=10; heterozygous=3; novel=7)]; SH3TC2 [20(homozygous=10), heterozygous=10, novel=4)]; MFN2[13(heterozygous=13, novel=2)]; PMP22 [11(duplications=2, deletion=1, heterozygous=8)]. Less common: PRX(3), GJB1(5), GJB(1), DYNC1H1(1), NTRK1(1), SURF1(1), SLC25A46(1), SBF2(1), SCN11A(1), SCN9A(1), SPG11(3), PLEKHG5(4), NEFL(5), NEFH(1), MTMR2(2), MME (1), MED25(2), MORC2(2), MPZ(1), NAGLU(1), NDRG(1), PKNP(1), LRSAM1(1), LITAF(1), JPH1(1), INF2(1), HSPB1(1), HSPB8(2), HK1(2), GARS(1), FIG4(1), FGD4(1), DHTKD1(4), AARS1(2), ATP1A1(1), DNM2(2), VCP(2), YARS1(1). Positive family history=36(33.0%). Distal lower limb(LL) and upper limb involvement=81 and 42 respectively, proximal LL weakness=16. Sensory loss in 25, sensory ataxia=15, tremors in 22. Other features: Retinitis pigmentosa(2 with PRX mutations), optic atrophy[(3, MFN2, PRX and SLC25A46)], sensorineural hearing loss[5 (SH3TC2=3, MFN2=1, SLC25A46=1)], ptosis and ophthalmoparesis[8 (SH3TC2=2, one each of MTMR2, PLEKHG5,NAGLU,MFN2, HSPB8, AARS1), tongue fasciculations[17(MFN2=2, PMP22=3, SH3TC2=3 and one each of MTMR2, DNM2, DHTKD1, MED25, LRSAM1, LITAF, PLEKHG5, PRX, DNM2). Icthyosis=3, nystagmus=2. Novel variants: GDAP1(4 frameshift(c.361delG, c.497_498delAC, c.500_501delCA, c.807delA) and 3 missense (c.691C>T: p.Pro231Ser, c.742G>T: p.Asp248Tyr, c.818G>T:p.Arg273Leu), SH3TC2 (two frameshift (c.1096_1097delGT, p.Thr366SerfsTer5 and c.1773delG, p.Leu592TrpfsTer53) and one each nonsense(c.1267G>T, p.Glu423Ter) and splice site(c.385+1G>A) variant and MFN2(c.716A>C; p.His239Pro and c.982G>A; p.Ala328Thr). Nerve biopsy(n=21) showed demyelinating changes in 15 and axonal in 6.

Conclusions:
This is the first Indian study describing the clinical features and mutation pattern in a large cohort of genetically confirmed Charcot-Marie-Tooth disease, highlighting salient clinical manifestations and the genetic spectrum. Several novel mutations have been identified and will need further studies.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Charcot-Marie-Tooth, Genetic spectrum, Clinical manifestations, India, CMT

Genetic Diagnosis in the Korean Patients with Inherited Peripheral Neuropathies

Poster No:
P 139

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Introduction:
Genetic cohort studies involving more than a thousand participants have been performed in many countries, but no such studies have been reported in Korea. Therefore, this study was performed to identify pathogenic mutations and to characterize clinical features according to the genetic causes.

Methods:
This cohort study was performed to identify the genetic causes in more than 1,200 Korean IPN families with variable subtypes. Molecular genetic screenings were performed by several methods, such as 17p12 duplication/deletion test by multiplex PCR, whole exome sequencing (WES), and targeted sequencing. In addition, phenotypic features were compared among patient groups with specific gene mutations.

Results:
This study identified genetic causes in 57 genes with the genetic diagnostic rate of 61.7%. Among the genetically diagnosed families, *PMP22* defects (including duplication and point mutations) were most frequently identified (53.9%), and then causative mutations were identified in *GJB1* (13.8%), *MFN2* (7.3%), *MPZ* (5.5%), and *NEFL* (2.1%). The frequency of families with recessive phenotypes was very low at 4.1%. Correlation of onset ages and disease durations with clinical severities showed different patterns according to defected genes. CMT1E, *MPZ*, and *MFN2* groups particularly showed early onset-severe and late onset-mild phenotypes.

Conclusions:
This study identified pathogenic or likely pathogenic mutation in 763 of 1,236 IPN families (genetic diagnostic rate of 61.7%). As the first cohort analysis on IPN patients in Koreans, this study expanded phenotypic spectrums in many genes.

References:
Yes

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Charcot-Marie-Tooth disease, Inherited peripheral neuropathies, cohort study, Korean

Incomplete Penetrance in Patients with Charcot-Marie-Tooth Disease

Poster No:
P 140

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Introduction:
Although Charcot–Marie–Tooth disease (CMT) has shown a loose genotype-phenotype correlation, it is commonly regarded as a simple disease that follows Mendelian inheritance well. However, it is known that mutations in several genes, such as *BSCL2* or *MFN2*, occasionally have shown incomplete penetrance. This study investigated Korean CMT families with presumptive incomplete penetrance.

Methods:
We examined Korean CMT families to identify genetic causes, then, analyzed families with incomplete penetrance or considerable differences in clinical severity within intrafamilial members having same mutation.

Results:
Incomplete penetrance or significant phenotypic differences were observed in patients with *MFN2*, *BSCL2*, *GARS1*, and X-linked genes. The p.N88S in *BSCL2* was observed in 7 families, and 6 of 22 individuals with the mutation showed no symptoms, indicating a high rate of incomplete penetrance (27.3%). While, the p.S90W in *BSCL2* identified in a large family showed well segregation with the affected individuals. For *MFN2* mutations, presumptive incomplete penetrance was observed in six families having one of p.H128R, p.R259H, p.R280H, p.R364Q, and p.L699P mutations. In a large family with the p.D200N in *GARS1*, the mutation was segregated with affected individuals, but an elderly woman showed very mild symptom (almost intact). In X-linked genes, approximately 10% of individuals with causative mutation were asymptomatic or very mild, where, they all were women.

Conclusions:
This study suggests roles of modifier genes in CMT phenotypes, as previously reported. Some genes showed interestingly mutation site-specific patterns. The milder symptoms and wide phenotypic expressivity in women compared to men in X-linked genes are probably related to heterozygous states (hemizygous in men) and X chromosomal inactivation.

References:
Yes

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Charcot-Marie-Tooth disease, Incomplete penetrance , wide phenotypic expressivity

Diverse phenotypic spectrums of PNMHH patients with *MYH14* mutation

Poster No:
P 141

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Introduction:
The *MYH14* (MIM 608568) gene encodes a member of the nonmuscle myosin heavy-chain II family that affects cytoskeletal actin and regulate cell motility, polarity, and mitochondrial function. 1 Mutations in *MYH14* have been reported to cause autosomal dominant non-syndromic deafness 4A (DFNA4A; MIM 600652).

Methods:
Clinical information included assessments of deep tendon reflex, muscle atrophy, and motor and sensory impairments. Nerve conduction studies of the median, ulnar, peroneal, tibial, and sural nerves were conducted using standard methods with surface stimulation and recording electrodes. Lower extremity magnetic resonance imaging including DTI and axial T2-weighted Dixon sequence was performed.

Results:
In the present study, we identified a second Korean family with the same *MYH14* p.R941L mutation. The affected individuals exhibited PN, HL, Ho, and myopathy, with phenotypes similar to those for the previously described Korean PNMHH family. Audiological studies showed bilateral sensorineural HL, with greater impairment at high frequencies. Hoarse voice was present in both affected individuals, but paresis of the vocal cords was not found. The affected individuals exhibited distal leg muscle atrophy. MRI showed abnormal fatty infiltration and muscle atrophy in the lower extremities similar to the findings in the previous Korean family, and sequential muscle involvement according to the disease duration was also observed. These reasons for the wide phenotypic spectrum of the PNMHH patients are still valid, but it may also be partly due to differences in race- or individual-specific genetic backgrounds, including genetic modifiers.

Conclusions:
In this study, we recommended that mutational screening for *MYH14* be performed when PN and HL with or without sensory disturbances occur together in a patient.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: PNMHH, Korean, MYH14, Phenotype, whole-exome sequencing

Perspectives and factors affecting the ability of CMT adolescents to live their lives

Poster No:
P 142

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Introduction:
CMT is a genetic disorder that affects muscle weakness, sensory impairment, hand and foot deformity. Children with CMT had an impact on their physical, psychosocial and school or work limitation. Some of them can overcome those limitation using different techniques to make them maintain their self-confidence. Adolescent is the period that vulnerable to adjust to the difference and identity from other people. Family and society are important to encourage the patient living and doing activities as much as they can. Aim of this study is to demonstrate the factors and perspectives of self-confidence in adolescent with CMT, along with their caregivers that enable patients to adjust and live their lives.

Methods:
This is a cross-sectional, qualitative descriptive study during December 2022 to May 2023. Data collection include demographic data, clinical manifestation, occupation or education were reviewed. A semi-structured interview about 1) perspectives of CMT on lifestyle 2) perspectives of physical, emotional and social self-care and 3) self-awareness were recorded and analyze.

Results:
Forty adolescent with CMT and their caregiver were recruited. The age of patients range from 10 to 24 years old. Majority of adolescent with CMT live their lives actively and have self-confidence. Factors associated with self-confidence are family support, sufficient income, access to the educational or working system.

Conclusions:
Adolescent with CMT is can overcome their physical and psychosocial limitation by several factors. The perspective of patients, families support, and opportunity from society is essential. The multidisciplinary care team to understand and recognize the needs is crucial for guiding the patient for further management.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Perspectives , CMT adolescents

Allele-specific CRISPR/Cas9 knockout of dominant FUS-FTD/ALS mutations in human iPSC-neurons.

Poster No:
P 143

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Institutions:
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Introduction:
Targeted knockout of a mutant allele could be therapeutic in many dominant neurogenetic diseases. Targeting a mutation itself is attractive, but often untenable due to diversity of mutations, absence of PAMs, or poor discrimination between mutant and wildtype alleles. Over 60 dominant mutations in fused in sarcoma (FUS) have been linked to ALS and FTD. Rather than target individual mutations, we have identified common non-pathogenic single nucleotide polymorphisms (SNPs) in the coding sequence of FUS. Targeting these SNPs would allow for knockout of any mutant FUS allele while leaving the normal allele intact. Based on these SNPs' frequencies across human populations, optimization of just four gRNAs could treat 64% of patients.

Methods:
To quantify editing in a disease-relevant system, we engineered a panel of human iPSCs with isogenic FUS mutations in a background heterozygous for both FUS coding SNPs. In each line, we tagged GFP and Halo to the endogenous FUS alleles, resulting in a yellow signal in unedited cells, and a red or green signal when the GFP- or Halo-tagged alleles are knocked out, respectively.

Results:
Phenotypically, wildtype FUS and mutants in the FUS prion-like domain reside in the nucleus, while mutants in the FUS NLS mislocalize to cytoplasmic stress granules. gRNAs targeting each of the four SNP alleles demonstrate high editing efficiency and specificity in iPSCs, with corresponding allelic mRNA and protein knockdown. Differentiation to motor neurons demonstrates that indels in the mutant FUS allele prevent the mislocalization phenotype.

Conclusions:
These studies demonstrate a therapeutic approach for FUS-FTD/ALS via SNP-targeted editing. Next we are delivering Cas9/gRNA directly to differentiated iPSC-neurons in order to asses editing efficiency and specificity in the context of neuron-specific DNA repair pathways and deep phenotyping our isogenic mutant panel using single molecule fluorescence and FUS-pulldown to explore how different FUS mutations lead to distinct cellular pathologies.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Fused in Sarcoma, ALS, CRISPR, Single Nucleotide Polymorphism, iPSC

GENOTYPE-PHENOTYPE CHARACTERISTICS OF VIETNAMESE PATIENTS DIAGNOSED WITH CHARCOT-MARIE-TOOTH DISEASE

Poster No:
P 144

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Introduction:
Charcot-Marie-Tooth (CMT) is one of the most common hereditary neuropathies. Identifying causative mutations in CMT is essential as it provides important information for genetic diagnosis and counseling prognostication and optimal management of the patients' disability.

Methods:
A total of 31 patients were prospectively recruited. The CMT diagnosis was made based on symptoms, clinical signs and electrodiagnostic evaluation. The clinical profiles of these patients were documented. The MLPA reactions were performed using SALSA MLPA Probe-mix P033 (CMT1A), P405 (CMTX), P406 (CMT2B), P143 (CMT2A), and P353 (CMT4). The targeted NGS panel of PMP22, MPZ, EGR2, NEFL, MFN2, GDAP1, GARS, MTMR2, GJB1, RAB7A, LITAF were designed and synthesized by xGen Predesigned Gene Capture Pools.

Results:
The proportion of male and female patient was 1.6:1. The disease largely started with weakness (26/31, 83.9%). Onset was observed within the first two decades of life with motor difficulty (26/31, 83.9%). Most patients exhibited typical clinical phenotypes, including symmetrical distal muscle weakness and atrophy, sensory impairments, decreased or absent deep tendon reflexes, pes cavus and/or joint deformities. Nerve conduction studies helped categorized patients into demyelinating (51.6%), axonal (38.7%) and intermediate CMT (9.7%). Genetic testing confirmed the causative gene in 9 demyelinating CMT (56.3%) and 4 axonal CMT (26.7%). The molecular detection rate by using the combination of MLPA and NGS in this CMT cohort was 41.9% (13/31). The most frequent causative gene alteration was PMP22 (29%), followed by MFN2 (6.5%). Five families agreed to take part in pedigree analysis. Two de novo variants NEFL (c.64 C>A, p.P22T) and PMP22 (c.281delG, p.94Afs*17) were identified in two families. For eighteen patients, the clinical diagnosis of CMT could not be confirmed genetically.

Conclusions:
The results of this study provide preliminary genetic data in Vietnamese CMT patients; and also illustrate the difficulty in making a positive genetic diagnosis in more than half of the patients.

References:
Yes

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References 4:
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Grant Support: Scientific Research Foundation of University of Medicine and Pharmacy at Ho Chi Minh city, Viet Nam

Keywords: Charcot-Marie-Tooth disease, genetic mutation, next-generation sequencing (NGS), multiplex ligation-dependent probe amplification (MLPA), de novo variants NEFL

Skin Biopsy As A Diagnostic Tool For Hereditary ATTR Amyloid Neuropathy In The UK.

Poster No:
P 145

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Introduction:
The introduction of gene silencing therapy for hereditary transthyretin (ATTRv) amyloidosis has revolutionised treatment for this previously fatal disease and the diagnosis of neuropathy is critical for access to this treatment. In minimally symptomatic early neuropathic disease (especially in ATTRv Met 30) where neurophysiology is normal, skin amyloid deposits have been demonstrated to be a marker of ATTRv amyloid neuropathy with intraepidermal nerve fibre density (IENFD), a marker of disease progression. We aimed to study the usefulness of skin biopsy in the diagnosis of UK ATTRv patients and to assess the influence of this on accessing gene silencing therapy.

Methods:
53 patients had skin biopsies performed between July 2021 and October 2022. Patients had two 3mm punch skin biopsies taken 10cm above the lateral malleolus, each 2cm apart. These were stained for amyloid (if positive, were typed by immunohistochemistry) and for IENFD.

Results:
A total of 59 skin biopsies were performed since July 2021, with 6 patients having a repeat biopsy. The T60A variant represented the highest number of cases at 27% closely followed by the V30M and V122I variants. The average age of the patients sampled was 57.5 years. Neurophysiology was normal in 62% of cases. From available results, 48% of cases had an abnormal IENFD result, 37% had positive amyloid staining and 24% had both. These results allowed 27% of these patients to start gene silencing therapy.

Conclusions:
Skin biopsy represents a useful, minimally invasive method for detecting amyloid deposits and small nerve fibre loss. Importantly, it permitted early diagnosis of amyloid neuropathy and commencement of gene silencing therapy in patients who would otherwise not have been eligible. As T60A and V122I are the commonest pathogenic TTR variants in the UK, with patients often presenting with cardiomyopathy, early diagnosis of amyloid neuropathy is crucial for therapy decisions.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: ATTRv, Skin biopsy, Amyloid neuropathy

Analysis of mitochondria-related neuropathy from clinically suspected Charcot-Marie-Tooth patients and mitochondrial diseases

Poster No:
P 146

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Introduction:
Peripheral neuropathy in mitochondrial diseases may vary from a subclinical finding in a multisystem syndrome to a severe, even isolated, manifestation in some patients. The purpose of this study is to identify causative mutations in mitochondria-related nuclear genes in patients with suspected hereditary peripheral neuropathy, and clarify how many of the cases diagnosed with mitochondrial disease have mutations in the causative genes of neuropathy.

Methods:
From May 2012 to Dec 2017, we collected 2695 cases with suspected CMT, whereas PMP22 duplication/deletion was excluded in advance for demyelinating CMT cases. On the other hand, 80 cases of suspected mitochondrial disease were collected from May 2013 to May 2022. Genetic analyses were performed using DNA microarrays, next-generation sequencing-based gene panel sequencing, and whole-exome sequencing. We performed further genetic analysis targeting 167 mitochondrial-related nuclear genes among a group of patients clinically suspected of pure or complex hereditary peripheral neuropathy and mitochondrial diseases.

Results:
In patients with suspected CMT, mitochondria-associated neuropathy was identified in 194 of 2695 patients (7%), not only MFN2, GDAP1, and COA7, established causative genes for CMT, but also POLG, SCLA2, MTPAP, HADHB, SURF1, and C12orf 65 genes were detected. In cases attributed to them, other neurological abnormalities consisting of encephalopathy, mental retardation, optic atrophy, and deafness were also found. In cases of suspected mitochondrial disease, the gene responsible for mitochondria-associated neuropathy was detected in 5 of 80 cases (6%), POLG, TWNK, RRM2B, OPA3, and ADCK3.

Conclusions:
We have identified mitochondria-associated gene mutations in a population of patients with CMT disease and mitochondrial disease. Because mitochondrial dysfunction often causes polyneuropathy, targeted screening of mitochondria-related nuclear genes should be considered for patients with complex inherited axonal polyneuropathies with CNS dysfunction and unexplained multisystem disorders.

References:
No

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References 2:

References 3:

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Grant Support: Research Committee of Ataxia, Health Labour Sciences Research Grant, the Ministry of Health, Labour and Welfare, Japan (201610002B) Japan agency for Medical Research and development (AMED) (201442014A, 201442071A, 17929553, JP22ek0109468h003) JSPS KAKENHI

Keywords: mitochondrial disease, CMT

Effect of leuprorelin of spinal and bulbar muscular atrophy in South Korea: 3-year observational study

Poster No:
P 147

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Introduction:
Spinal and bulbar muscular atrophy (SBMA) is an X-linked motor neuron disease characterized by progressive bulbar and limb muscle weakness with atrophy. The androgen suppression therapy by leuprorelin has been used to ameliorate disease progression with limited evidence. The aim of our study was to longitudinally evaluate the effect of leuprorelin in Korean SBMA patients for 3 years.

Methods:
34 genetically confirmed SBMA patients were enrolled. All the patients received leuprorelin acetate every 12 weeks, for 3 years. The primary outcome was to observe the changes in the SBMAFRS-K and ALSFRS-R. We also longitudinally evaluated video fluoroscopy swallowing study, pulmonary function test and laboratory tests.

Results:
The mean age of treatment start was 55.4 years-old with a mean disease duration was 11 years. ALSFRS-R and SBMAFRS-K showed an annual decrease of 0.87 and 1.6 points for 3 years. However, there was statistically significant decrease of most of the subscores except for bulbar function. The penetration-aspiration score (PAS), showed a numerical improvement without statistical significance. We divided SBMA patients to mild and progressed groups and the subgroup analysis showed that mild patients with a better baseline functional score showed less decline of clinical scales compared to progressed patients.

Conclusions:
Leuprorelin was well tolerated in Korean SBMA patients without significant adverse events. We observed stabilization in the bulbar function of SBMA and this was clear in patients with higher baseline motor function. In conclusion, although leuprorelin showed modest effect in overall functions of SBMA, there was significant stabilization in the bulbar function and longer longitudinal studies are warranted to consolidate our data.

References:
No

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Grant Support:

Keywords: spinal and bulbar muscular atrophy, treatment, androgen suppression, bulbar, motor

Next-Generation Sequencing Uncovers Interesting Findings In Patients with Inherited Peripheral Neuropathies.

Poster No:
P 148

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Institutions:
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Introduction:
Inherited peripheral neuropathies (IPNs) are clinically and genetically heterogeneous. Next-generation sequencing technologies have increased the identification of disease genes and variants causing IPNs. Nevertheless, many patients diagnosed clinically as having IPNs evade accurate genetic diagnosis.

Methods:
The purpose of the study was to research the genetic cause of disease in a cohort of 20 IPN patients referred to our group from a diagnostic laboratory, where they remained unsolved following screening on targeted neurogenetic disease gene panels. Short-read whole-genome or whole-exome sequencing was performed, followed by co-segregation and/or functional studies where necessary.

Results:
Genetic diagnoses were achieved for seven patients. In a patient with an early-onset demyelinating IPN, a novel de novo missense GBF1 variant (NM_001377137.1: c.2932A>C, p.(Ile978Leu)) was identified. To date, GBF1 variants have only been associated with axonal neuropathies. MME variants were uncovered in three IPN patients. Of these, two patients harboured intronic variants, and subsequent reporter minigene splicing assays showed the variants resulted in altered MME splicing. Bi-allelic VWA1 variants were identified in an IPN patient with myopathic features; one variant a known 10 base pair ancestral duplication, the other a novel likely pathogenic missense variant (NM_022834.5: c.62_71dup, p.(Gly25Argfs*74); c.212T>C, p.(Leu71Pro)). In the sixth solved patient, known pathogenic bi-allelic COX20 variants (NM_198076.6: c.41A>G, p.(Lys14Arg); c.157+3G>C) were identified as the cause of disease through co-segregation with disease in the family. In the seventh patient, born to a consanguineous couple, a homozygous missense variant in a candidate disease gene was identified.

Conclusions:
The study highlights the utility of research next-generation sequencing and analysis, including trio analysis, where targeted gene panels did not achieve a genetic diagnosis. Analysis is ongoing for unsolved IPN patients, including structural variant and short tandem repeat expansion calling.

References:

No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Inherited Peripheral Neuropathies, Next-Generation Sequencing, Neuromuscular Disorders

A Comprehensive Update of the Inherited Neuropathy Consortium (INC) of the Rare Diseases Clinical Research Network

Poster No:
P 149

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Introduction:
The Inherited Neuropathy Consortium (INC) is composed of 20 sites that evaluate patients with Charcot-Marie-Tooth disease (CMT) and maintain data pulled from clinical visits in a standardized manner.

Methods:
Clinical information from patient visits is electronically maintained in a database housed under control of a centralized data management center. All sites are actively seeing patients, and DNA samples from INC sites are tested for identification of potential new forms of CMT and genetic modifiers of CMT1A. Current projects include: Natural History Evaluation of Charcot-Marie-Tooth disease (with particular emphasis on CMT1B, CMT2A, CMT4A, and CMT4C); Genetics of CMT; Development of CMT Peds Scale for Children with CMT; Charcot-Marie-Tooth Disease Infant Scale (CMTInfS); and Digital Measures of Physical Activity, Gait and Balance in CMT.

Results:
These projects have helped create validated outcome measures to use in clinical trials. Additionally, over the past 11 years, the INC has identified over half of all genes currently known to cause CMT. The INC has evaluated 7,313 patients for the Natural History Evaluation of CMT; 2,893 of these patients also participate in the Genetics of CMT, 1,047 participate in the Pediatric study, 65 participate in the Infant study, and 232 participate in the Digital Measures study. All these studies are actively recruiting. The INC also partners with patient advocacy groups (PAGs) to enhance patient knowledge and establish connections between patients, researchers, and physicians. These groups include the Muscular Dystrophy Association, the Charcot Marie Tooth Association, CMTUK, ACMT-Rete, Hereditary Neuropathy Foundation, CMT Research Foundation, and Telethon from Italy.

Conclusions:
Through development of validated outcome measures, curation of an extensive longitudinal CMT database, and investigation into new genetic factors of CMT, the INC has contributed to the current understanding of the causes and outlook of CMT for medical and patient communities alike.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: The Inherited Neuropathy Consortium is part of the NIH Rare Diseases Clinical Research Network (grant #1U54NS065712-01). The INC also receives funding from the Muscular Dystrophy Association and the Charcot-Marie-Tooth Association.

Keywords: Charcot-Marie-Tooth, CMT, Genetics , Neuropathy

A Specific Functional Complex of MPZ(P0) and PMP22 May Play a Role in Peripheral Neuropathies

Poster No:
P 150

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Introduction:
Myelin Protein Zero (MPZ) is an abundant adhesion protein within peripheral nerve myelin wraps. MPZ mutations cause CMT (Charcot-Marie-Tooth) disease. Whereas some MPZ mutations induce ER stress, other mutations may affect other functions of MPZ. Mutations in Peripheral Membrane Protein 22 (PMP22), including its gene duplication, account for most CMT cases. PMP22 is a tetraspan integral membrane protein expressed at high level in Schwann cells. It is unclear what function PMP22 provides or why an extra copy of wild-type PMP22 can cause dominant CMT1A. Interestingly, when highly expressed in non-Schwann cells, PMP22 accumulates in the ER and might potentially cause disease by eliciting ER stress. Here we show that PMP22 and MPZ form a strong and specific interaction.

Methods:
Co-immunoprecipitations experiments with chimeric MPZ and PMP22 proteins were used to find the structural basis of MPZ:PMP22 formation. Co-expression experiments were used to find whether MPZ alters PMP22 subcellular distribution.

Results:
PMP22 forms a robust interaction with MPZ in both HEK293 and RT4 rat Schwannoma cells. PMP22 and MPZ each belong to larger protein families, which include the PMP22 homologs EMP1,2,3, and MPZ-like proteins and NaV beta subunits, respectively. Our studies show that among different family members, only PMP22 forms a complex with MPZ and only MPZ forms a complex with PMP22. Using a chimeric approach with different PMP22 or MPZ family members, we found the determinant for complex formation is the transmembrane domain of MPZ. Finally, we found that co-expression of MPZ with PMP22-GFP shifted its localization from predominantly ER compartments to the cell surface.

Conclusions:
MPZ may potentially accelerate degradation of the ER-pool of PMP22. These studies provide a physical and mechanistic link to the two major proteins involved in the pathogenesis of CMT and imply that complex formation may play an important disease relevant role.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: myelin protein zero, PMP22, Charcot-Marie-Tooth disease, ER stress, immunoprecipitation

Phenotypical and Genotypical Variability of Patients with Charcot-Marie-Tooth Disease in a Register Study at Charité Berlin, Germany

Poster No:
P 151

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Introduction:
Charcot-Marie-Tooth disease (CMT) is the most frequent hereditary peripheral neuropathy. Symptoms often start in early childhood and progress over time, leading to disability and loss of self-sufficiency. There are over 100 known mutations known but no causal therapy available up to now. The characterization of phenotypical variability and natural disease history is essential for present and future therapy development and clinical trial preparation.

Methods:
At Charité Berlin, we used an extensive battery of clinical scores, laboratory examinations, and electrophysiological examinations to characterize patients with CMT during 2022. Furthermore, we established a biobank for skin biopsies as well as fibroblast cultures for future genomic, proteomic, and morphological analyses.

Results:
We collected over 40 patients with clinical diagnosis of CMT, out of which about 70% received a genetic diagnosis. Variants of 11 causal genes were identified, including 6 variants of unknown significance. The average age of onset was 19 years with a range from 0 to 55 years, and clinical severity as well as phenotypes varied greatly even within single mutations.

Conclusions:
CMT is a genetically and phenotypically diverse disorder. There is an urgent need to better understand this variability in order to predict disease course, identify possible modifiers of disease severity, and prepare for clinical studies.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: This project was supported by financial reimbursement/travel support by Alnylam Pharmaceuticals Inc, research funding by Alnylam Pharmaceuticals Inc., and Pfizer Pharmaceuticals, and research funding by Deutsche Gesellschaft für Muskelkranke (DGM)

Keywords: CMT, registry, phenotype, clinical characterization, natural history

Adult-onset and Fast-progressing Charcot-Marie-Tooth Disease Chameleons To Be Aware of

Poster No:
P 153

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Introduction:
At the point of first clinical contact, it can be diagnostically challenging to differentiate between an inherited and acquired peripheral neuropathy. Often the proband presents without an accompanying positive family history, the clinical syndrome may be progressing rapidly and there may be features present that would otherwise be considered atypical for an inherited neuropathy, such as non-length dependent weakness and denervation.

Methods:
We present 6 patients with genetically confirmed CMT (2 NEFH, 3 MME and 1 TFG), with adult-onset and fast progressing disease. Prospective clinical and neurophysiological data were obtained during annual natural history study visits.

Results:
The mean age of symptom onset was 37.8yrs (range 33-49) and despite an average disease duration of only 12.8yrs (range 7-16), 50% of patients (3/6) required a wheelchair or stick for mobility. There was universal significant proximal involvement early on in the course of their disease and 3 out of 6 patients had evidence of a non-length dependent neuropathy. All sporadic cases had CSF examinations and investigations for inflammatory causes of neuropathy and one patient had IVIG therapy prior to achieving a genetic diagnosis.

Conclusions:
Certain CMT subtypes may mimic acquired neuropathies and it is important to keep both acquired and inherited neuropathies in the differential diagnosis while the diagnosis is being established.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Charcot-Marie-Tooth disease, Non-length dependent neuropathy, Adult-onset, Axonal subtype

De Novo Frameshift Variant in Acetylcholinesterase in a Girl with Axonal Polyneuropathy and Neuropsychiatric Disorder

Poster No:
P 154

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Introduction:
ACHE encodes acetylcholinesterase, which catalyzes the breakdown of acetylcholine and terminates synaptic transmission at the neuromuscular junction (NMJ) and synapses of cholinergic neurons. According to gnomAD, ACHE is constrained in predicted loss-of-function variants in a control population that lacks severe, early-onset phenotypes (pLI score = 0.998). We identified a de novo frameshift variant in ACHE in a patient with a subacute axonal polyneuropathy and neuropsychiatric disorder.

Methods:
Medical history and phenotype was clinically evaluated. Trio exome analysis was done to investigate causative variants and Sanger sequencing was done to validate the findings.

Results:
We report a sporadic case of a 13 years old girl with a history of behavioral disorders, epilepsy, and intermittent phlogistic signs in lower limbs since the age of 1 year. At 11, she developed paraparesis with subacute progression and concomitant neuropsychiatric condition. Electroneuromyography showed sensory-motor axonal polyneuropathy. Trio exome analysis identified a de novo frameshift variant in ACHE (c.902dup, ENST00000428317), absent in gnomAD, which is predicted to cause a premature stop codon [p.(Ala302Serfs*40)]. No other potentially pathogenic variants in known disease genes or rare homozygous variants were segregating in the family.

Conclusions:
To our knowledge, this is the first time a heterozygous predicted loss-of-function variant in ACHE is described. A complete loss of acetylcholinesterase activity at the NMJ by loss of COLQ, which anchors the esterase, causes congenital myasthenia. Interestingly, genes associated with acetylcholine function at the NMJ, SLC5A7 and SYT2, have been recently associated with both myasthenic and motor neuropathy phenotypes. Our case might add evidence that acetylcholine disfunction at the NMJ is involved with peripheral neuropathy and highlights a potential novel disease gene. Further functional studies and collaborative efforts to identify matching cases are needed to unravel this intriguing and complex syndrome.

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Yes

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Montes-Chinea NI, Guan Z, Coutts M, et al. Identification of a new SYT2 variant validates an unusual distal motor neuropathy phenotype. Neurol Genet. 2018;4(6):e282.

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Keywords: novel gene discovery, ACHE, acetylcholinesterase, axonal neuropathy, genetics

CMT and sport activities: a worldwide survey

Poster No:
P 155

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Introduction:
Charcot-Marie-Tooth (CMT) disease is the most common genetic neuromuscular disease. The typical symptomatology involves distal muscle weakness, provoking different degrees of disability. The practice of recreational activities could promote wellness and quality of life in many neuromuscular diseases. The aim of this study is to investigate sport practice among the CMT population.

Methods:
We designed an online questionnaire for CMT patients to investigate sport practice and recreational activities and we spread it worldwide with the support of the Italian CMT Association, the European CMT Federation and other patient advocacy groups. We included all hereditary neuropathies. Then, we analyzed the data with an Excel format.

Results:
A total of 290 CMT people responded to the survey (F/M ratio: 2,7). The most frequent age-range was 46 to 55 years (30%). 46,9% of them were from Italy, the remaining were from Europe, United States and Australia. The most of them stated to practice home exercises (28,3%) or individual physical therapy (23,8%). Other mentioned activities were gym, water activities or outdoor activities. Only the 3,8% stated to not practice any activity. The frequency of the exercises was 2,8±1,9 days per week. No significant differences have been observed among age range. People with a higher schooling stated to practice more activities.

Conclusions:
The majority of CMT persons stated to perform many different wellness activities, from individual rehabilitation activities to gym practices. Although the schooling seems to be an important factor, age and sex do not affect these habits. If we consider that the OMS guidelines suggest a minimum of 150 minutes of a moderate aerobic activity per week, most of them does not reach the minimum of practice. Since literature lacks of studies about sport practice in people with CMT, we need further study to understand what kind of activity is beneficial and raise awareness in CMT population.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: CMT, sport acrtivities, quality of life, survey, wellness

Characteristics and evolution of the Charcot-Marie-Tooth hand: an observational study over 2 years

Poster No:
P 156

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Introduction:
Charcot-Marie-Tooth (CMT) disease is the most common hereditary neuropathy, with an overall prevalence estimated at 10-28/100 000. The typical symptoms mainly involves the feet in the lower limbs and the hands in the upper limbs. There is a lack of knowledge about the upper limbs and the disease progression over time. Moreover, there are few validated measurement tools, and they often have limitations. The aim of this work is to analyze the characteristics of the CMT hand and monitoring the progression over time.

Methods:
At the baseline, we have analyzed the hand of 113 patients with neuropathy, afferent to our integrated outpatient for hereditary neuropathies. We then included in the study patients with another hand evaluation after 12 and 24 months (n=26). The outcome measures were thumb opposition test (TOT), Sollerman Hand Function Test (SHFT), Tripod Pinch, Hand Grip, CMT neuropathy score. Moreover, we used an innovative tool, an engineered glove that measure the dexterity (Alberti et al., 2015).

Results:
At the baseline, we confirmed that all parameters collected are lower comparing to normal subjects as already demonstrated (Prada et al., 2018). The long term analyses showed that after 1 year, even if an impairment is visible in the means of every measure, no one of them is significant. After 24 months, SHFT starts to be significantly impaired (differently if dominant or non-dominant hand) and some dexterity parameters diminish significantly.

Conclusions:
The hands impairment is an important problem for the quality of life and it should be more deeply studied to find rehabilitative or occupational solutions. We observed that all the measures are impaired in these patients. Progression of strengths and articularity is slower than dexterity. Further studies are needed to improve the understanding of the dysfunction mechanisms.

References:
Yes

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Grant Support:

Keywords: Charcot-Marie-Tooth, Upper limbs, Disease progression, Hand, Outcome measures

Towards In Vivo Studies Of C12ORF65/MTRFR Deficiency In Mitochondrial Translation In Neurons

Poster No:
P 157

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Introduction:
The nuclear gene C12ORF65 encodes mitochondrial translation release factor rescue-1 (MTRFR), a small protein vital for proper mitochondrial translation that acts as a mitoribosome release factor when translation is terminated. Patients presenting with recessive C12ORF65 mutations often have optic and peripheral neuropathies characteristic of Behr's syndrome, Leigh syndrome, and Charcot-Marie-Tooth disease (CMT). However, the underlying mechanisms and neuronal sensitivity have not yet been explained.

Methods:
To fully understand how C12ORF65 deficiency leads to neurodegeneration, a mouse model mimicking patient phenotypes is necessary. Presently, we are developing a conditional knock-out mammalian model to study in combination with our loss-of-function and transgenic models of C12ORF65 deficiency. These mice will clarify the genetic mechanism and cell-specificity of this peripheral neuropathy. By crossing the conditional knock-out model with various Cre-strains we will induce C12ORF65 deficiency in specific cell types including retinal ganglion cells and peripheral motor and sensory neurons.

Results:
Our current models consist of a null mutation and a premature truncation of C12ORF65 on the endogenous Chromosome 5, which result in embryonic lethality in homozygotes. The two Cre-inducible transgenes express versions of the human C12ORF65 sequences inserted into a safe harbor locus on Chromosome 6. One transgene is of the fully functional wildtype human gene (WTKI), the other is a mutated human gene (3K>A) with predicted 60% functionality. The transgenic mice partially rescue the embryonic lethality of the premature truncation, however this is not a good disease model.

Conclusions:
Understanding C12ORF65 deficiency will provide insight into how mitochondrial translation plays a role in neuropathy and neurodegeneration. C12ORF65 is critical for survival in mice and plays an important role in neuronal health. We are also working on creating a conditional knock-out model to better model this disease. This multifaceted approach of modeling C12ORF65 deficiency will inform gene therapy approaches and provide a preclinical platform for future studies.

References:
No

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Grant Support:

Keywords: Mitochondria , Translation , Neurodegeneration , Peripheral Neuropathy, Mouse Models

The first large deletion of ATL3 in a patient presenting with sensory polyneuropathy, detected by the CovCopCan software.

Poster No:
P 158

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Introduction:
Hereditary sensory neuropathies (HSN) are a heterogenous group of peripheral neuropathies affecting the sensory nerves, with variable severity and onset. Few heterozygous mutations in ATL3 have been described in patients presenting with Hereditary-Sensory-Neuropathy-IF (HSN1F), a subtype of HSN, following an autosomal dominant transmission mode.

Methods:
In our study, we used targeted NGS and the CovCopCan bioinformatic tool to analyze NGS data from a patient presenting with sensory polyneuropathy symptoms.

Results:
We discovered thus, the presence of a deletion of around 3kb including exons 11 and 12 of ATL3. In addition, a bioinformatic analysis of sequences revealed the presence of transposable elements at the breakpoints' area, suggesting that Non-Allelic-Homologous-Recombination mechanism could be responsible for this SV. Moreover, thanks to the electronic microscopy (EM), severe rarefaction of the myelinated fibers and demyelinating-remyelinating process were observed in the patient's nerve biopsy. EM also pointed out an abnormal aspect of the endoplasmic reticulum and Golgi apparatus.

Conclusions:
This is the first time that a large deletion in ATL3 has been identified and we highlight the importance of not only searching for pointed mutations or small indels in this gene, but also for structural variations. Implementing SVs search, patients' diagnosis could be improved, not only for patients suffering from HSN but also for other inherited diseases.

References:
No

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References 2:

References 3:

References 4:

Grant Support:

Keywords: Hereditary sensory neuropathies, Structural Variants, ATL3, CovCopCan, Diagnosis

Plasma Neurofilament Light Chain Concentration in RFC1-Related Disease: a Multicentre Cross-sectional Study

Poster No:
P 159

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Introduction:
Recently, biallelic intronic AAGGG repeat expansions in the replication factor complex subunit 1 (RFC1) gene have been identified as the cause of cerebellar ataxia, neuropathy, vestibular areflexia syndrome (CANVAS) and a frequent cause of late-onset ataxia and sensory neuronopathy. Disease severity and course appear to be highly variable and, given the lack of insight into the pathomechanisms of the disease, no potential biomarker has been identified yet. Neurofilament light chains (NfL) are a promising biomarker in both central and peripheral nervous system disorders. In this multicentre cross-sectional study, we aimed: 1) to evaluate NfL serum levels in a cohort of RFC1 CANVAS and disease spectrum patients, and 2) to correlate NfL serum concentrations with disease severity.

Methods:
Sixty-one patients with genetically confirmed RFC1 CANVAS and disease spectrum and forty-eight healthy controls (HCs) were enrolled in the study from six different Neurological Centres. Serum NfL concentrations were measured by single-molecule array assay technique.

Results:
Serum NfL concentration was significantly higher in patients carrying biallelic RFC1 expansions compared to age-and-sex-matched HCs ($p < 0.0001$). Median NfL concentrations were also significantly higher in CANVAS patients with clinical cerebellar involvement compared to patients without cerebellar dysfunction (27.46 vs 22.51, p= 0,0260). NfL levels had a significant correlation with age at blood sampling in both RFC1 CANVAS and disease spectrum (p=0,0036, r= 0,3676) and HCs (p=0,0020, r= 0,4353). Serum NfL concentration did not appear to correlate with disease duration and need of walking aid.

Conclusions:

Serum NfL concentration was significantly higher in RFC1 CANVAS and disease spectrum patients than in HCs. Longitudinal studies are warranted to investigate the possible role of serum NfL in disease monitoring.

References:
No

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References 3:

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Grant Support:

Keywords: RFC1, CANVAS, Nfl, biomarker

Studying myelin alterations in CMT4H with label-free nonlinear vibrational microscopy

Poster No:
P 160

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Introduction:
Charcot Marie Tooth disease (CMT) is among the most common inherited neurological disorders, affecting the peripheral nervous system. CMT4H is an autosomal recessive demyelinating form of Charcot-Marie-Tooth, for which we have identified FGD4 as the causative gene. The disease is characterized by excessive redundant myelin abnormalities defined as myelin outfoldings. We have developed a faithful mouse model, with conditional ablation of fgd4 in Schwann cells (Fgd4SC-/-) as a reliable tool to study pathomechanisms in CMT4H. Our goal was to use label-free polarization-resolved microscopy (Coherent Anti Stokes Raman Scattering (CARS)) and immunofluorescence approaches to study myelin organization in this model. We present here preliminary investigations of CARS imaging on teased nerve fibers from our mouse model of demyelinating CMT4H disease.

Methods:
Using immunofluorescence and CARS imaging on ex vivo teased fibers from proximal and distal regions of sensori-motor (mixed:sciatic and tibial) and sensory (saphenous) nerves from Fgd4SC-/- mice, we studied myelin alterations and lipid organization of myelin sheath.

Results:
Interestingly, we demonstrate a decrease of the internodal length and myelinated fibers' thickness in distal parts of mixed nerves (tibial) from Fgd4SC-/- animals, as compared to the proximal part of the same nerve (sciatic). In pure sensory fibers, we noticed a proximo-distal increase in internodal length without marked changes in myelinated fiber thickness. Moreover, proximal sensory fibers' internodes are shorter in Fgd4SC-/- nerves than in WT. The tibial Fgd4SC-/- nerve fibers display a decrease in internode length and thickness of the myelin sheath, while Fgd4SC-/- sensory fibers internodes are only markedly shorter than WT. They also present a greater number of myelin outfoldings.

Conclusions:
Here, we show that CARS microscopy allows precise label-free imaging of the myelin sheath and its organization. Such new readouts can be a first step toward developing new non-invasive imaging tool for diagnosis of peripheral nerve pathologies.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: Fondation A.MIDEX, NEUROPOL Project

Keywords: CMT4H, FRABIN, Coherent Anti Stokes Raman Scattering, imaging, myelin outfoldings

Human IP3 receptor triple knockout stem cells are pluripotent despite altered mitochondrial metabolism

Poster No:
P 161

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Introduction:
Heterozygous variants in inositol 1,4,5-trisphosphate receptors (IP3R) type 3 cause demyelinating Charcot-Marie-Tooth disease (CMT). IP3Rs are ER calcium channels that are composed of three isoforms: IP3R1, IP3R2 and IP3R3, which have tissue-specific expression. We set out to create a model for elucidating cell type-specific functions of the human IP3 receptors and understand the pathogenesis of CMT. For this, we generated single and triple knockout (TKO) cell lines of induced pluripotent stem cells (iPSC) and studied the role of IP3Rs in stem cell survival, pluripotency and metabolism.

Methods:
We used CRISPR/Cas9 to knock out IP3R genes (ITPR1, ITPR2 and ITPR3) in iPSC. We confirmed editing with western blotting and RT-qPCR, and analyzed the resulting KO lines with gene expression panel and with embryonic body formation assay. Finally, we employed functional Ca2+ imaging and LC-MS and U-13C labelled glucose fluxomics to assess IP3R function and metabolism.

Results:
Successful implementation of the desired gene editing events was demonstrated by the loss of protein production and IP3R mediated Ca2+ response in the generated cell lines. Comparable levels of pluripotency markers were identified between KO and control cell lines. The KO cell lines had similar differentiation potential compared with non-edited cells. However, we found a significant alteration in the mitochondrial metabolism as the TKO cells had a deficiency in their pyruvate utilization via pyruvate dehydrogenase (PDH), shifting towards pyruvate carboxylase pathway (PC).

Conclusions:
This study shows that IP3Rs are not essential for iPSC identity and pluripotency, but regulate iPSC metabolism. Loss of IP3Rs results in alteration of mitochondrial metabolism, with a shift towards the PC pathway. These changes may be relevant for the development of CMT when IP3R3 is defective. Our iPSC lines provide a robust model for elucidating how IP3R-mediated calcium signaling contributes to peripheral nervous system function.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: CMT, IP3 receptors, iPSC, Calcium signaling

Dominant Charcot-Marie-Tooth Disease Due To Heterozygous SLC12A6 Variants

Poster No:
P 162

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Introduction:
Biallelic variants in the potassium/chloride co-transporter gene SLC12A6 are known to cause a complex syndrome including axonal neuropathy, agenesis of the corpus callosum, neurodevelopmental defects and dysmorphism. Recently, dominant or de novo dominant variants have been proposed as causing Charcot-Marie-Tooth disease (CMT). We present a series of dominant SLC12A6-related CMT.

Methods:
Patients were clinically assessed at specialist neuromuscular centres and had genetic testing via gene panel, whole exome, or whole genome sequencing.

Results:
We identified 20 patients from 12 families with 10 different variants in SLC12A6. Mean age of patients was 51 years (range 17-83 years) and mean age of onset of disease was 24 years (2-52 years). 61% were male. The most common phenotype was intermediate CMT (CMTi, 44%), then CMT2 (38%) and distal hereditary motor neuropathy (19%). The phenotype was predominantly an uncomplicated, length-dependent CMT, although one family had facial weakness, restricted gaze and ptosis, which is seen in recessive disease. A further patient had intellectual disability. Variants reported are p.Ser647Pro (two families, one confirmed de novo case and segregating in one other family with dominant inheritance), p.Gly552Asp (2 families), c.2437-2A>G (1 family), p.Trp210Cys (1), p.Met282Lys (1), p.Thr482Ile (1), p.Pro569Ser (1), p.Ser1079Thr (1), p.Gly286Cys (1) and p.Asp640Gly (1). When classified by American College of Medical Genetics criteria, previously reported variants p.Ser647Pro and p.Gly552Asp are likely pathogenic and pathogenic respectively, and the remaining novel variants are of uncertain significance; work is being done to upgrade their status.

Conclusions:
To date, this is the largest series of patients harbouring heterozygous SLC12A6 variants causing CMT. This report confirms the pathogenic nature of heterozygous variants in the gene, and that the most common phenotype is CMTi, but age of onset ranges from infantile to late-adult onset, suggesting a broad phenotypic spectrum. Further work is needed to understand disease mechanisms and explore any genotype-phenotype correlations.

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Yes

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Grant Support:

Keywords: CMT, SLC12A6, Charcot-Marie-Tooth, genetics, phenotype

Patient Reported Disease Burden in the Accelerate Clinical Trials in Charcot-Marie-Tooth Disease (ACT-CMT) Study.

Poster No:
P 163

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Introduction:
The Charcot Marie Tooth Disease-Health Index (CMT-HI) is a patient-reported disease burden measure that has been developed and validated for use in therapeutic trials in CMT. As part of a multicenter, international clinical trial readiness study (ACT-CMT), individuals with CMT1A (ages 18 to 75 years), are undergoing serial clinical outcome (COA), electrophysiologic and imaging biomarker assessments. Participants are completing the CMT-HI at each visit, to capture their longitudinal perspective on the impact of CMT1A.

Methods:
Two hundred and fifteen adults with CMT1A enrolled in the ACT-CMT study are undergoing serial COAs including the CMT-HI, the CMT Functional Outcome Measure (CMT-FOM), CMT Neuropathy Score (CMTNSv2R), CMT Exam Score (CMTES/CMTES-R) and Overall Neuropathy Limitations Scale (ONLS). The CMT-HI total score (CMT-HI (T)), CMT-HI subscores and correlations of the CMT-HI with measures of neurologic impairment and function were analyzed using baseline data. Changes in the CMT-HI (T) over 12 months were assessed using a paired t-test. A p-value < 0.05 was considered significant.

Results:
CMT1A participants are 44.5±15 years old (58% female). The CMT-HI (T) at baseline was 25.7±18.8 (range 0-91.9; 100 reflecting maximal disease burden). Disease burden was greater among females than males (CMT-HI (T) 29.1±19 versus 20.9±17.4, $p = 0.001$). The CMT-HI (T) correlated with age ($r=0.18$, $p=0.007$), and with physical function as measured by the CMT-FOM ($r=0.54$, $p < 0.0001$). CMT-HI (T) results also correlated with measures of neurologic impairment and disability including the CMTNSv2R ($r=0.5$), CMTES/CMTES-R ($r=0.53$/$r=0.54$), and ONLS ($r=0.55$).

Conclusions:
Patient-reported disease burden in CMT1A as measured by the CMT-HI is associated with measures of neurologic impairment, disability and physical functioning, but is overall relatively stable over 12

months. Females report a higher disease burden, which requires further study. This emerging data from the ACT-CMT study will inform granular design of future clinical trials in CMT1A.

References:
No

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References 2:

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Grant Support: Supported by NIH grant # NIH 1 U01 NS109403 to David Herrmann

Keywords: CMT, CMT-Health Index, Outcome Measure, Disease Burden, Clinical Trials

Genetic characterisation of a clinically suspected cohort of inherited neuropathies in India

Poster No:
P 164

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Introduction:
Inherited neuropathies are a heterogenous group of genetic neuropathies who have varied phenotypic and genotypic features. Neuropathy may be the sole or major phenotypic feature or part of a wider neurological or multisystemic disease. We aim to describe the genetic characterisation of a clinically suspected cohort of hereditary neuropathy in India.

Methods:
All clinically suspected patients with hereditary neuropathy were recruited prospectively in the MRC-funded International Centre for Genomic Medicine in Neuromuscular Diseases (ICGNMD) cohort from a tertiary care hospital in north India. All participants gave informed consent. All patients underwent deep phenotyping and nerve conduction studies (NCS). Genetic testing involved CMT1-MLPA for all exons of PMP22, MPZ and GJB1, whole exome sequencing (WES), and PCR testing for Friedreich ataxia. Virtual diagnostic panels were applied to exome data and ACMG criteria was applied to classify identified variants.

Results:
63 probands and 9 affected relatives were included in the analysis. CMT1-MLPA for all exons of PMP22, MPZ and GJB1 was done on 14 probands and 3 were solved (PMP22 deletion-2, HNPP; PMP22 duplication-1, CMT1A). PCR for Fredrich's ataxia were tested in 5 probands and 3 probands were positive. Undiagnosed inherited neuropathy cases (57 probands) underwent singleton WES. Results of WES are available for 16 probands and 7(44%) were solved. Nine were unsolved with no tiered pathogenic or likely pathogenic variants. WES results are awaited in 41 probands. Among the WES solved cases, the genes involved are three probands with SH3TC2 (CMT4C), one each of HSPB1 (CMT2F), PRX (CMT 4F), GJB1 (CMTX1) and ADA2 (DADA).

Conclusions:
The genetic testing pipeline of single gene tests and WES in a deeply phenotyped cohort followed by segregation analysis improves the diagnostic rate of genetic neuropathies.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: Medical Research Council (UK) strategic award to establish an International Centre for Genomic Medicine in Neuromuscular Diseases (MR/S005021/1)

Keywords: neuropathy, CMT, hereditary neuropathy

Combined morphological and Expression studies in Motor Nerve biopsies identify a pTDP-43 endophenotype in a subgroup patients presenting with peripher

Poster No:
P 165

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Introduction:
We previously shown that motor nerve biopsy may be used for an early diagnosis in lower motor neuron syndromes (LMNS). Most importantly, we have more recently demonstrated that the detection of phosphorylated TAR DNA-binding protein-43 (pTDP-43) deposits within motor nerve axons and of Swann Cells cytoplasm may represent an useful pathologic biomarker for the distinction between Amyotrophic Lateral Sclerosis (ALS) and motor neuropathy patients, even before axonal degeneration occurs. Specifically, pTDP-43 axonal accumulation was detected in 56 ALS cases (98.2%) versus seven in non-ALS samples (30.4%), while concomitant positive Schwann cell cytoplasmic staining was found in 40 ALS patients (70.2%) versus four non-ALS cases (17.4%). Therefore, although our study demonstrates a high specificity of pTDP-43 aggregates for the diagnosis of ALS, our results also imply that a pTDP-43 pathology can be detected in a non-neglectable percentage of non-ALS cases.

Methods:
Histopathologic criteria of motor neuron disease (MND) and motor neuropathy (MN) were applied by two independent evaluators, who were blind for clinical data. TDP-43 and phosphorylated TDP-43 (pTDP-43) were evaluated by immunohistochemistry (IHC). Genetic analysis was performed with NGS

Results:
Herein we aim to describe the clinical and pathological features of 9 patients which unexpectedly presented with clinical and histological features of a peripheral neuropathy associated with a pTDP- 43 pathology within motor nerves. Our study identifies a subgroup of non-ALS patients displaying a peripheral chronic, predominantly motor axonal neuropathy with distinguishing clinical and pathological features. Next Generation Sequencing genetic analysis are undergoing in order to identify the molecular basis of these cases

Conclusions:
Our findings show that a pTDP-43 pathology may be detected in patients presenting with a non-inflammatory motor neuropathy and support the existence of a continuum between motor neuron diseases

and a specific subgroup of PNS disorders. Further studies are needed to better understand the role of pTDP-43 aggregates in non-ALS neuromuscular disorders

References:
Yes

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References 2:
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References 3:

References 4:

Grant Support:

Keywords: pTDP-43 , aggregates, axonal neuropathy, motor neuropathy, CMT

Novel variant in the UBA1 gene as cause of progressive motor neuronopathy

Poster No:
P 166

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Introduction:
Ubiquitin-like modifier-activating enzyme 1 (UBA1) gene on chromosome Xp11.3 encodes a ubiquitin activating enzyme [1]. Mutations in UBA1 are associated with X-linked Spinal Muscular Atrophy (SMAX2) causing hypotonia, areflexia, and multiple congenital contractures associated with loss of anterior horn cells and infantile death [2]. It is also linked to Non-Kennedy's X-linked spinal bulbar muscular atrophy that causes weakness starting in the 4th to 5th decades of life [3]. Here we present a case of a novel UBA1 mutation associated with progressive motor neuropathy/neuronopathy beginning at age 10 years.

Methods:
The patient is a fraternal twin born at 32 weeks gestation. Motor milestones were slightly delayed. He was a slow runner and had poor balance, but At 13 he developed weakness in his upper extremities. He was noted to have primarily distal motor weakness with mild proximal thigh involvement at his first clinical exam. There was no sensory involvement. EMG/NCS showed evidence for a predominantly motor, axonal peripheral neuropathy. Patient was followed longitudinally with yearly clinic visits and genetic testing was pursued.

Results:
Genetic testing revealed a novel UBA1 variant of uncertain significance (VUS) (c.500C>T;p.Thr167Ile). His mother was found to be a carrier. His brother, who did not have similar symptoms, did not carry this mutation. No other affected family members were identified. Variant is located in the inactive adenylation domain of the protein. Known pathogenic variants have been reported in the active adenylation domain. Patient has progressed significantly to essentially quadriplegia being unable to ambulate and needing a frame to stand. He has no sensory findings.

Conclusions:
This case of VUS in the UBA1 gene displays features of SMAX2 although most prior cases have died in infancy. The variant in this patient has not been reported elsewhere. Functional studies of this variant may show partial loss of function consistent with the milder phenotype.

References:
Yes

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References 3:
Khani M, Nafissi S, Shamshiri H, et al. Identification of UBA1 as the causative gene of an X-linked non-Kennedy spinal–bulbar muscular atrophy. Eur J Neurol. 2022,00:1-8

References 4:

Grant Support:

Keywords: CMT, Hereditary motor neuropathy, UBA1

Vestibular function selective involvement in CANVAS: audiological and MRI study of the eight cranial nerve

Poster No:
P 168

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Introduction:
Cerebellar ataxia, neuronopathy and vestibular areflexia syndrome (CANVAS) is an inherited adult-onset slowly progressive neurological disease due to a repeated biallelic intronic AAGGG pentanucleotide expansions in the RFC1 gene. Aim of our study was to quantitatively investigate with a comprehensive battery of tests the auditory and vestibular functions in individuals with complete or incomplete CANVAS-spectrum disorder.

Methods:
We enrolled 15 genetically confirmed CANVAS patients (10 men, mean age 66.5 years), with sensory axonal neuronopathy. The mean AAGGG expansion size was 768.8 (SD 171.8) for the shorter allele and 1059.0 (SD 319.4) for the longer allele. Auditory function was tested identifying the hearing threshold at 0.5, 1, 2 and 4 kHz. Vestibular function was tested trough video-oculography with warm and cold caloric stimulation, video heat impulse test stimulating the three semicircular canals and measuring the optokinetic reflex at 20°/sec and 40°/sec. Eleven patients with sensory axonal polyneuropathy (5 hereditary, 6 idiopathic) were used as control group (7 men, mean age 69.2 years). 3T-MRI evaluation of eight cranial nerve (DRIVE sequences) was also performed in CANVAS patients.

Results:
CANVAS patients showed significant impairment in all the measures of vestibular function (p ranging from 0.007 to <0.001). Auditory function in CANVAS patient did not correlate with any vestibular measure. Comparison between right and left side did not show significant differences for all measures. Controls showed significant higher hearing threshold (p=0.007). MRI showed an atrophy of vestibular nerve in 10/16 patients (62.5%), while auditory nerve was normal in all subjects.

Conclusions:
The results of our study showed a striking and selective involvement of vestibular function with sparing of auditory functions in CANVAS patients when compared to other axonal polyneuropathies. These results point to a possible selective pathogenetic mechanism involving the eight cranial nerve that may represent a diagnostic biomarker for axonal neuropathies prompting genetic testing.

References:

No

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References 2:

References 3:

References 4:

Grant Support:

Keywords: CANVAS, Vestibulary function, Vestibular nerve

Reduced cross-sectional area at nerve ultrasound in genetically confirmed CANVAS patients

Poster No:
P 169

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Introduction:
Nerve cross-sectional area (CSA) of patients affected with axonal neuropathy usually shows normal value. In this study we measured nerve CSA with ultrasound (US) in a group of patients with complete or incomplete CANVAS (Cerebellar Ataxia with Neuropathy and Vestibular Areflexia Syndrome) and biallelic RFC1 repeat expansions. We compared nerve CSA from CANVAS patients with a CSA from a group of patients with idiopathic axonal neuropathy (AxPN), hereditary axonal neuropathy (CMT2) and Friedreich ataxia (FRDA).

Methods:
We enrolled 14 CANVAS patients (8 men, mean age 66.9 years, mean disease duration 10.8 years), affected with sensory axonal neuronopathy. Mean AAGGG expansion size of the RFC1 gene was 702.3 (SD 174.2) for the shorter allele and 942.2 (SD 269.2) for the longer. Controls consisted of: 16 AxPN (mean age 71.0 years, 8 male), 7 CMT2 (mean age 47.9 years, 4 male), 14 FRDA (mean age 34.1, 6 male). Nerve US was performed at median, ulnar, sciatic, sural and tibial nerves and brachial plexus, bilaterally.

Results:
The nerve CSA from CANVAS patients was significantly smaller than the CSA from both patients with AxPN, CMT2, and FRDA at all sites (p ranging from $p=0.021$ to $p< 0.001$. RFC1 expansion did not correlated with CSA at any site.

Conclusions:
The results of the present study showed a widespread CSA reduction along the whole course of peripheral nerves in CANVAS patients, both at upper and lower limbs and at proximal and distal sites. Notably, nerve CSA of CANVAS patients was significantly lower than other axonal polyneuropathies and neuronopathy (FRDA) thus suggesting a peculiar morphological pattern. In conclusion, widespread reduction of nerve CSA represents a hallmark of CANVAS.

References:
No

References 1:

References 2:

References 3:

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Grant Support:

Keywords: CANVAS, Ultrasound, Neuronopathy

Cellular Effects Of A Novel CMT2A Mitofusin-2 Mutation And In Vitro Phenotype Correction With Mitofusin-1

Poster No:
P 170

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Introduction:
Mutations in the MFN2 gene have been linked to Charcot-Marie-Tooth Type 2A (CMT2A) peripheral neuropathy. MFN2 encodes for Mitofusin-2, a mitochondrial outer membrane protein responsible for the normal fusion of mitochondria. Mutated Mitofusin-2 has been shown to cause abnormal mitochondrial aggregation which can be resolved upon overexpression of homolog Mitofusin-1.

Methods:
To further study a novel MFN2 mutation (p.K357T) from a 4-year old patient, the MFN2K357T as well as MFN2WT and MFN1WT were cloned downstream of the CBh promoter. Subsequently, these constructs were expressed either separately or combined in differentiated SH-SY5Y cells.

Results:
Transfection with the MFN2K357T construct alone caused significant mitochondrial aggregation, while transfection with either the MFN2WT or MFN1WT construct, although they too induced a degree of mitochondrial aggregation (being higher in MFN1WT), they mostly displayed a non-aggregated phenotype with mitochondrial distribution along axons. Co-transfection with the MFN2K357T and MFN1WT constructs significantly shifted the MFN2K357T mutant phenotype towards a non-aggregated state. Furthermore, MFN2WT and MFN1WT co-transfection also reduced the degree of mitochondrial aggregation observed with MFN1WT transfection alone, suggesting a balancing effect of MFN2WT on overexpressed MFN1WT.

Conclusions:
Our findings support previous studies showing that MFN2 mutations cause mitochondrial aggregation leading to CMT2A development. Enhanced MFN1 expression may restore the MFN2/MFN1 balance, rescuing mitochondrial fusion in vitro, supporting further testing of MFN1 overexpression in vivo as a therapeutic strategy for CMT2A.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: CMT2A, Mitofusin 2, Mitofusin 1

RFC1 in an Australasian neurological disease cohort: extending the genetic heterogeneity and implications for diagnostics

Poster No:
P 171

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Introduction:
Cerebellar ataxia, neuropathy and vestibular areflexia syndrome (CANVAS) is a progressive, generally late-onset, neurological disorder associated with biallelic pentanucleotide expansions in intron 2 of the RFC1 gene. The locus exhibits substantial genetic variability, with multiple pathogenic and benign pentanucleotide repeat alleles previously identified.

Methods:
To determine the contribution of pathogenic RFC1 expansions to neurological disease within an Australasian cohort and further investigate the heterogeneity exhibited at the locus, a combination of flanking and repeat-primed PCR (RP-PCR) was used to screen a cohort of 242 Australasian neurological disease patients. Patients whose data indicated large gaps within expanded alleles following RP-PCR, underwent targeted long-read sequencing to identify novel repeat motifs at the locus. To increase diagnostic yield, additional probes at the RFC1 repeat region were incorporated into a targeted neurological disease gene panel to enable first pass screening of the locus for all samples tested on the panel.

Results:
Within the Australasian cohort, we detected known pathogenic biallelic expansions in 15.3% (n=37) of cases. Forty-five samples tested indicated the presence of biallelic expansions not known to be pathogenic. A large proportion of these (84%) showed complex interrupted patterns, suggesting these expansions are likely comprised of more than one repeat motif including previously unknown repeats. Long-read sequencing identified three novel repeat motifs in expanded alleles. Here we also show that short read sequencing can be used to reliably screen for the presence or absence of biallelic RFC1 expansions in all samples tested using the targeted neurological disease gene panel.

Conclusions:
Our results show that RFC1 pathogenic expansions make a substantial contribution to neurological disease in the Australasian population and further extend the heterogeneity of the locus. To accommodate the increased complexity, we outline a multi-step workflow utilising both targeted short- and long-read sequencing to achieve a definitive genotype and provide accurate diagnoses for patients.

References:
No

References 1:

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References 3:

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Grant Support:

Keywords: CANVAS, RFC1, ataxia, sensory neuropathy, STR

The INSPIRE Study: A RandomIzed Study to Evaluate Pharmacodynamic and Clinical Benefit of AT 007 in Patients with Sorbitol Dehydrogenase Deficiency

Poster No:
P 172

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Introduction:
SORD is the second enzyme in the two-step polyol pathway, an alternative glucose metabolism pathway. Patients with SORD Deficiency are unable to process sorbitol, leading to accumulation of this toxic metabolite in blood and tissues. SORD Deficiency presents clinically as an axonal, predominantly motor polyneuropathy leading to progressively worsening disability. In vitro and in vivo studies have recently demonstrated that treatment with AT-007 leads to decrease of sorbitol in blood in a SORD deficient animal model and in cultured human fibroblasts from SORD Deficiency patients. A recent pilot study evaluated the safety and effect of AT-007 treatment on blood sorbitol levels in a cohort of patients with SORD Deficiency.

Methods:
This ongoing INSPIRE study is a multicenter, randomized, double-blind, placebo-controlled investigational trial. The study is designed to assess the pharmacodynamic (PD) efficacy of AT-007 treatment, as well as the clinical benefit of long term administration of AT 007 to patients with SORD Deficiency. The clinical endopoints utilize a series of functional, patient-reported, and clinical outcome measures including CMT-FOM (10 Minute Walk Run Test [10MWRT], total, and subdomain scores) and CMTHI. Safety and PK of AT-007 are also evaluated.

Results:
Patients (16-55 years old) with SORD Deficiency were stratified according to gender and based on their 10MWRT score at baseline entry to the trial. Patients were randomized in a 2:1 ratio to active AT-007 20 mg/kg once daily (QD) or placebo. Blinded safety review at >6 months from the first patient dosed supports AT-007 as safe and well tolerated to date.

Conclusions:

In summary, SORD Deficiency is a severe and progressive neuropathy caused by abnormally elevated levels of sorbitol. The ongoing placebo-controlled Phase 3 study is evaluating AT-007 treatment and impact on clinical outcomes in SORD Deficiency patients.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: This study is funded by Applied Therapeutics

Keywords: SORD Deficiency, Sorbitol, CMT

VIRTUAL CMT INFANT TODDLER SCALE (vCMTInfS); A REMOTE EVALUATION OF INFANTS/TODDLERS WITH CMT

Poster No:
P 173

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Introduction:
The CMTInfS measures CMT disability from birth to 4 years. Many CMT subtypes present in early childhood, an ideal time to intervene before clinical sequelae resulting from demyelination and axonal loss. Because many infants/toddlers have difficulty accessing CMT clinics, we have developed and are testing a virtual CMTInfS (vCMTInfS) to evaluate patients remotely using this scale

Methods:
Patients with caregivers are evaluated remotely using Zoom or equivalent after providing informed consent. vCMTInfS is evaluated identically to the in person instrument. Parents/caregivers are provided with a list of necessary items including beads and string, blocks, button/buttonhole, markers and paper, book, Sophie Giraffe toy, specimen jar and tennis ball. The remote examiner directs activities comprising the 15 item vCMTInfS with assistance from the parent, while observing the child's capabilities. The evaluations will be video-recorded for review by master trainers.

Results:
vCMTInfS was performed remotely on a 3 year old child with CMT4B3, caused by a pathogenic variant in the SBF1 gene. All scale components were completed and observed by the evaluator. The child was scored a 6 (z-score of 0.5; mild) on the CMTinfS. He could role supine to prone, sit, crawl, squat and recover, run, throw a ball, build tower, scribble, unscrew lid, and string beads. He needed to hold his mother's hand to stand on one foot, could tear unfolded but not folded paper and was unable to button.

Conclusions:
This case demonstrates the feasibility of performing vCMTInfS as if we were performing the evaluation in clinic. Additional infants will be evaluated and presented. vCMTInfS will enable evaluation of infants/toddlers with CMT otherwise unable to be seen in clinics expanding our ability to perform natural history studies and identify the clinical onset of CMT in our youngest patients.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: : The Inherited Neuropathy Consortium is part of the NIH Rare Diseases Clinical Research Network (grant #1U54NS065712-01)

Keywords: Outcome, infant, virtual, CMT

Drug repurposing screening identified novel autophagy enhancers for CMT2

Poster No:
P 174

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Introduction:
Small heat shock proteins (sHSP) promptly respond to misfolded proteins and aggregates by facilitating their refolding or promoting their degradation through the ubiquitin-proteasome system or autophagy. sHSP sustain proteostasis in all kinds of cells, however mutations in HSPB1 and HSPB8 predominantly affect the peripheral nerves leading to the onset of axonal Charcot-Marie-Tooth neuropathies (CMT2). The CMT2L Hspb8K141N/K141N mouse model revealed axonal degeneration and muscular atrophy, axoplasmatic deposits with LC3II and p62/SQSTM1 accumulation. Moreover, iPSC-derived motoneurons (iMN) carrying the HSPB1_P182L or HSPB8_K141N mutation showed a reduction in LC3-positive autophagosome formation. The common deficits in autophagy point out at the importance of sHSP in this pathway.

Methods:
Hspb8K141N mouse embryonic fibroblasts (MEFs), endogenously expressing GFP-LC3, were exposed to a library of 2000 annotated compounds and natural products. By means of LC3 puncta quantification after 22h treatment, compounds that were able to enhance the autophagic activity compared to the canonical mTOR inhibition were selected for further validation. Neurite network density, mitochondrial morphology and protein expression were assessed further on iMN.

Results:
Chemically and functionally diverse molecules were selected for the conversion of the cytosolic LC3IB in its lipidated form LC3BII, while preserving the expression of ATG9A, a pre-autophagosome marker. Furthermore, the autophagy induction was confirmed by the activation of Unc-51-like autophagy activating kinase (ULK1). Treatment with the novel autophagy inducers alleviate stress during the differentiation promoting the neurite network development in the CMT2 iMN, increased the autophagosome formation and promoted mitochondria morphology changes.

Conclusions:
The sHSP mutations impair the autophagosome formation, eventually leading to neurotoxicity. The drug screen efficiently identified active compounds that rescue the autophagy defects in sHSP mutant lines and consequently resulted in the amelioration of the neuronal phenotype. In the future, we aim to validate the autophagy inducers on the CMT mouse model and pave the way for novel autophagy-based treatment for axonal CMT.

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Yes

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References 4:

Grant Support:

Keywords: Drug screening, sHSP, Autophagy, CMT2

Introducing routine diagnostic Whole Genome Sequencing into the clinic

Poster No:
P 175

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Introduction:
Recruitment to the 100,000 Genomes Project (100KGP), was completed in December 2018. Data from the project has provided thousands of families with a genetic diagnosis and is allowing development in all areas of genomic medicine, from diagnostics to treatments. From April 2022, whole genome sequencing (WGS) has been introduced as a diagnostic test in the UK National Health Service (NHS) for certain disease groups including Charcot Marie Tooth disease (CMT). However, with opportunities come challenges that clinicians face when working with WGS data in a clinical setting. Aim: To asses the introduction of routine WGS for inherited neuropathy panel testing in our peripheral nerve clinics with special reference to clinician understanding and patient consent.

Methods:
We describe our practical experience of introducing routine diagnostic WGS into our Peripheral Neuropathy Clinics.

Results:
All clinicians (including six consultants) needed updated training in consent procedures for WGS. This was achieved by online information being made available by the NHS diagnostic laboratory, by a virtual training seminar and through face-to-face training by a dedicated inherited neuropathy specialist nurse. All 6 consultants are now trained and comfortable obtaining consent for WGS. Since its introduction in April 2022, we have requested 40 WGS tests including 30 singleton, one duo and 9 trio. Out of 41 patients asked to consent only one has declined testing. One patient agreed to WGS diagnostic testing but declined participation in research.

Conclusions:
While WGS will increase the diagnostic yield for inherited neuropathies, utilising this service requires expert training for clinicians, particularly in the consent process with regards unexpected findings. Increased time in clinic will be required to achieve this and hence a dedicated nurse specialist or equivalent is essential to delivering this service safely and effectively.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: CMT, WGS

Postural Stability In Hereditary Neuropathy Patients: Studying The Role Of Somatosensory And Motor Involvement

Poster No:
P 176

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Introduction:
Balance impairment in Charcot-Marie-Tooth disease patients (CMT) is responsible for the increased risk of falling. Distal lower limbs weakness and reduction of tactile and proprioceptive sensitivity are the main factors affecting postural control, along with skeletal foot deformities and pain. However, the role of these systems in determining postural instability is not clear, yet. This study aims to investigate the influence of somatosensory deficits on static and dynamic balance in CMT patients.

Methods:
As of today, we compared three cohorts (as defined by neurophysiology): 12 patients with CMT, 11 neuromuscular motor patients (MOT, six with inherited motor neuropathy and five with distal myopathy) and eight healthy controls. All participants performed strength evaluation of lower limbs; goniometric measurement of ankle passive range of motion; evaluation of the plantar tactile sensory threshold with Semmes-Weinstein monofilaments; foot deformities evaluation with the Foot Posture Index; balance assessment with the Balance Evaluation Systems Test (BESTest). To detect the displacement of the center of pressure, some items of BESTest were also performed on static force platform. The second version of the CMT Neuropathy Score was used.

Results:
Somatosensory impairment was present only in CMT patients, while strength deficits were equally distributed in CMT and MOT patients. In balance assessment, CMT patients obtained lower average scores. CMT patients maintained the upright position with sensory deprivation (steady-state balance) with greater oscillations than MOT. This greater steady-state postural instability correlated with a higher tactile-pressure sensitive threshold, weaker distal muscles and a higher CMT Examination Score. Conversely, no statistically significant difference was found in reactive and proactive postural control (dynamic balance).

Conclusions:
Somatosensory impairment, net of motor involvement, plays a pivotal role on instability in CMT patients during steady-state conditions. Conversely, our results suggest that dynamic balance is mostly dependent on the integrity of the motor system.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Charcot-Marie-Tooth , Postural instability, Inherited neuropathies, Inherited myopathies

Real-World Effectiveness Of High-Dose Tafamidis On Neurologic Disease Progression In Mixed-Phenotype Variant Transthyretin Amyloid Cardiomyopathy

Poster No:
P 177

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Introduction:
Transthyretin amyloidosis is a rare disease that can be caused by mutations in the transthyretin gene and is now widely recognized as a spectrum of disease that can manifest as polyneuropathy, cardiomyopathy, or a mixed phenotype. Phenotypic expression depends on the particular amyloidogenic variant, amyloid deposition pattern, and multisystem involvement. Tafamidis is a first-in-class highly specific and selective stabilizer of both wild-type and amyloidogenic variants of transthyretin. Neurologic endpoints were not included in the cardiomyopathy development program of Tafamidis, necessitating the use of real-world approaches to assess the potential neurologic benefit of high dose tafamidis. The objective of this study is to assess neurologic disease progression before and after initiation of high-dose tafamidis in patients with mixed-phenotype variant transthyretin amyloid cardiomyopathy (ATTRv-CM) in a real-world setting.

Methods:
This retrospective cohort study will include at least 30 patients with mixed-phenotype ATTRv-CM who were treated with tafamidis 61 mg orally once daily. Patient data will be collected from baseline/initiation of tafamidis for at least 6 months. Assessments will include the following, as available in the medical record: neuropathy impairment score-composite score (NIS-CS), NIS-lower limbs (NIS-LL), polyneuropathy disability (PND) score, Medical Research Council (MRC) Scale for Muscle Strength, Charcot-Marie-Tooth neuropathy score v2 (CMTNS2), and modified body mass index (mBMI). Data analysis will be descriptive in nature given the real-world data collection. If multiple measures are available in the record, baseline scores will be compared with scores during the treatment period.

Results:
Available interim results will be provided at the time of the meeting.

Conclusions:
This is the first study to our knowledge to report real-world effectiveness of high-dose tafamidis on neurologic disease progression in mixed-phenotype ATTRv-CM patients.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: Pfizer Inc.

Keywords: ATTR, tafamidis, real-world data, chart review, outcomes

A Human Gene Regulatory Network For Schwann Cells

Poster No:
P 178

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Introduction:
Studies of inherited peripheral neuropathies (Charcot-Marie-Tooth disease) have identified over 100 disease genes. Some of these genes encode transcription factors (TF) that regulate a network of other genes involved in demyelinating neuropathy. Despite the immense progress, there remain many cases where genetic causes of neuropathy is not known, and some mutations may affect the noncoding parts of the genome. To provide resources to uncover noncoding variants emerging from Whole-Genome Sequencing (WGS) analysis, we are developing a gene regulatory network for human Schwann cells.

Methods:
We have employed human Schwann cell chromatin accessibility data based on published single cell ATAC-seq data to identify enhancers and promoters. We then link transcription factors (TF) to regulatory elements using motif analysis. To validate the gene regulatory network model, we are employing peripheral nerve ChIP-seq data to evaluate the network predictions of TF binding.

Results:
As an initial test of the model, we have found expression quantitative trait loci (eQTL) variants associated with variations of gene expression in human tibial nerve, some of which are located within noncoding regulatory elements and are predicted to disrupt TF regulation of their target genes. We have also found a significant number of TF binding sites are corroborated by experimental data. In addition, we have developed several data sets identifying patterns of TF binding in Schwann cells to identify transcription factor collaborations that drive Schwann cell gene expression.

Conclusions:
The human Schwann regulatory network provides a map of noncoding regulatory networks in the Schwann cell epigenome that can be used to interpret whole genome sequencing data from cases of Charcot-Marie-Tooth disease. Noncoding regulatory elements may be affected by either point mutations, indels, or structural variants that are either genetic causes and/or modifiers of CMT. This model may also be useful in analysis of Genome-Wide Association Studies (GWAS) to find disease associations for genomic variants.

References:
No

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Grant Support: NIH R21 NS127432

Keywords: Schwann, noncoding, CMT, transcription, enhancer

Forward Genetic Screen Identifies MTMR6 as Potential Suppressor of Charcot-Marie-Tooth Type 2C

Poster No:
P 180

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Introduction:
The cation channel transient receptor potential vanilloid 4 (TRPV4) is a cell surface-expressed calcium-permeable cation channel that mediates cellular morphology and function. Dominant missense mutations of TRPV4 cause distinct diseases, but the pathogenic mechanisms remain unclear. Previously published work shows that expression of a neuropathy-causing TRPV4 mutant (TRPV4R269C) causes dose-dependent neuronal dysfunction and axonal degeneration in Drosophila.

Methods:
Using an unbiased forward genetic screen in Drosophila, we identified myotubularin related protein 6 (MTMR6) as a potent suppressor of TRPV4 pathology. The MTMR gene family codes for phosphoinositide phosphatases implicated in other forms of CMT. Decreased expression of Mtmr6 leads to increases in autophagic vesicles and enhances autophagic response in a stress-induced environment. Here, by utilizing Drosophila as a model system, we will define autophagy disruption in CMT2C by analyzing autophagic vesicles distribution and axonal trafficking in motor and sensory neurons.

Results:
Since MTMR6 has been implicated in early secretory and autophagic pathways, we are investigating the interaction between TRPV4, MTMR6, and autophagy. Preliminary data suggests that mutant TRPV4 inhibits autophagic vesicle formation, suggesting a role for TRPV4 in autophagy.

Conclusions:
Ongoing studies are focused on the mechanisms of TRPV4-mediated autophagy inhibition and the role that MTMR6 plays in this process.

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Yes

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Grant Support:

Keywords: Autophagy, TRPV4 cation channel, Drosophila

Patient-Reported Psychosocial Outcomes in Charcot-Marie-Tooth Disease. A Hereditary Neuropathy Foundation (HNF) Survey

Poster No:
P 181

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Introduction:
Charcot-Marie-Tooth (CMT) disease encompasses a spectrum of hereditary peripheral nerve disorders associated with progressive muscle weakness, sensory loss, neuropathic pain and limb deformities. This analysis utilizes patient-reported outcomes to explore underrecognized contributors to disease burden impacting quality of life in CMT.

Methods:
HNF's Global Registry for Inherited Neuropathies recruited participants with CMT from North and South America, Europe, and Australia to complete 3 discrete online surveys exploring demographics (N=1679), lifestyle (N=851), and psychosocial factors (N=251). Validated PROMIS® scales generated T-scores describing pain quality, life satisfaction, and social isolation. Chi-square analysis, Pearson's product-moment correlation, and Wilcoxon rank sum tests were applied to evaluate the relationships between variables.

Results:
A majority of respondents (81.6%) reported pain in the past 7 days, with a mean (SD) severity of 4.2±2.5 out of 10. Pain quality was neuropathic-type in 63.95% of participants endorsing pain. Pain severity was negatively correlated with life satisfaction ($r=-0.253$, $p=0.00059$) and positively with social isolation ($r=0.167$, $p=0.02597$). Compared to those with non-neuropathic pain, patients with neuropathic pain reported lower life satisfaction ($p=0.03558$) and higher social isolation ($p=0.005967$). Of 465 patients reporting use of prescription medications for neuropathic pain, 135 (29.03%) were prescribed opioids. Respondents with pain reported 10% lower engagement in >30 minutes of daily exercise vs. those without ($p=0.013$).

Conclusions:
These patient-reported data underscore the impact of pain on psychosocial outcomes in CMT. High rates of opioid use for neuropathic pain in the survey population suggest opportunities for prescriber and patient education regarding evidence-based pain treatment. Suboptimally treated pain may contribute to worse social isolation, health behavior, life satisfaction and sedentary lifestyles. Interprofessional treatment of neuropathic pain may improve psychosocial and physical outcomes in CMT. Note: The first 2 authors contributed equally to this work.

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Yes

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Grant Support: 2020 Million Dollar Bike Ride Grant Program, Orphan Disease Center, University of Pennsylvania

Keywords: Charcot-Marie-Tooth disease, hereditary motor and sensory neuropathy, Patient reported outcomes, neuropathic pain, opioids

The gain of function SCN9A spectrum disorder: complex painful phenotype

Poster No:
P 182

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Introduction:
Dominant gain-of-function variants causing hyperpolarization of the Na(v)1.7 sodium channel in the nociceptive and sympathetic neurons are known to cause erythromelalgia and paroxysmal extreme pain disorder, whilst recessive loss-of-function are linked to absence of pain perception, ulcers, and bone dysplasia.

Methods:
Clinical, laboratory and electrophysiological data were analyzed. Whole exome sequence test was performed on proband.

Results:
A 20-year-old male patient presenting a complex disorder characterized by excruciating pain episodes, heat intolerance, hypohidrosis and difficulty walking due bilateral acetabular dysplasia. His pain started in his first year of life. He was able to walk only at with 30 months of age. He is the only son from healthy and unrelated parents. To ease his pain, he remains immersed in a barrel of fresh water all day. The skin on his lower limbs was hyperkeratotic. On neurological examination he has mild sensory impairment in lower limbs and normal reflexes globally. NCS revealed sensory action potentials with normal amplitudes and mild reduction on the NCV (70-90% of normal value). Sural nerve biopsy revealed thinly myelinated fibres. Muscle biopsy showed predominant type 2 atrophy. Sweat test was abnormal. Sympathetic skin response was absent throughout. WES revealed a class 5 variant (ACMG) in the SCN9A gene (NM_002977.3: c.701T>C ; p.Ile234Thr) within domain I/S4-S5 linker.

Conclusions:
The I234T is a well characterized variant that causes channel gain-of-function. We present a patient with a complex phenotype including painful neuropathy,developmental dysplasia of the hip and mild muscle abnormalities. The astonishing need for the patient to remain constantly emersed in water reflects the severity of his symptoms.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: sodium channel, neuropathy, small fibre, NGS

Healthcare and welfare information on patients with Charcot-Marie-Tooth disease in Japan: an epidemiological study based on CMT Patient Registry.

Poster No:
P 183

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Introduction:
The natural history of patients with Charcot–Marie–Tooth disease (CMT) and the healthcare and welfare surrounding them in Japan is still unclear. This study aimed to clarify the natural courses, medical conditions, and problems in daily life and medical care of patients with CMT in Japan.

Methods:
We have developed an online patient registration system, CMT Patient Registry (CMTPR). CMT patients or their families directly enter into the system and fill out questionnaires, asking about the age of onset, symptoms, treatment, and healthcare and welfare services that patients receive. We analyzed answers obtained from 303 patients (males: 162, females: 141, median age: 48 years old, range: 2–89, interquartile range: 31.5–60) who registered for CMTPR from April 2015 to April 2021.

Results:
The median onset age of CMT was 15 (range: 0–78, interquartile range: 10–37). Genetic testing was performed in 65%. The causative gene mutations, in order of prevalence, were duplication of the PMP22 gene (44.2% of the patient with genetic testing), GJB1 gene mutation (8.6%), MFN2 gene mutation (8.1%), and MPZ gene mutation (6.6%). Seventy-six percent of the patients had regular visits to medical facilities. Five percent of patients had no history of hospital visits. Fifteen percent of all patients needed assistance with daily activities due to motor function impairment in the upper extremities, and 25% required assistance due to lower limb impairment. Age and gender were not related to the need for assistance for walking or other behavior. Of the 267 adult patients, 18% had difficulty working due to reasons related to the disease.

Conclusions:
This is Japan's first nationwide epidemiological study with healthcare and welfare information on patients with CMT. Although online registries were subject to selection bias, we could collect daily life information from patients who do not regularly attend healthcare facilities.

References:
No

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References 3:

References 4:

Grant Support: This research was supported by AMED under Grant Number JP19ek0109271h0003 and Grants-in Aid from the Research Committee of CNS Degenerative Diseases, Research on Policy Planning and Evaluation for Rare and Intractable Diseases, Health, Labour and Welfare

Keywords: Charcot-Marie-Tooth disease, CMT Patient Registry, questionnaire survey, registry research, epidemiological studies

A heterozygous 9q34 deletion containing SPTAN1 has a variable penetrance in a family with Hereditary Motor Neuropathy

Poster No:
P 184

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Introduction:
Haploinsufficiency of SPTAN1 due to nonsense mutations is a known pathomechanism in Hereditary Motor Neuropathy (HMN), although heterozygous knock-out mice do not present with an overt phenotype. SPTAN1 nonsense mutations in humans are known to have a variable phenotypic presentation with incomplete penetrance.

Methods:
WES-based CNV detection was employed in a large-scale reanalysis effort of the Solve-RD Horizon 2020 EU project. The encountered deletion was confirmed and segregated using SNP-array. Patient-derived lymphoblasts and fibroblasts were established. Protein expression levels of affected genes (SPTAN1, GLE1, SET) were evaluated using Western Blotting. RNA levels of SPTAN1 are being evaluated using qPCR.

Results:
Using WES-based CNV detection, we encountered a heterozygous deletion of the 9q34 locus encompassing SPTAN1 in a multigenerational family with HMN. We subsequently confirmed the deletion size using SNP-array and performed segregation analysis, revealing non-penetrance of the CNV in two non-affected family members. Additionally, the severity of the phenotype is variable between family members. Using patient-derived lymphoblasts and fibroblasts, we determined expression of SPTAN1, GLE1 and SET at the protein level, showing no apparent difference between patient and control lines.

Conclusions:
Although haploinsuffiency of SPTAN1 is a known disease mechanism, protein levels in lymphoblasts and fibroblasts do not seem to be altered upon heterozygous SPTAN1 deletion in a multigeneration HMN family. Heterozygous full gene deletions and nonsense mutations in the same gene might have differential pathomechanisms. Further work on this family will help to ascertain whether this is the case for SPTAN1.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: SPTAN1, Copy Number Variation, haploinsufficiency

SCREEN4PN: Evaluation Of Therapeutic Compounds For Charcot-Marie-Tooth Disease Using Patient-Derived Induced Motor Neurons

Poster No:
P 185

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Introduction:
Charcot-Marie-Tooth (CMT) disease is the most common peripheral neuropathy, with over 2,5 million patients globally. Most therapeutic studies for CMT are in a laboratory or pre-clinical phase, with only one clinical study reaching phase III for the most common form of CMT, type 1A. SCREEN4PN is an induced pluripotent stem cell (iPSC) testing platform being developed to efficiently test new therapeutic compounds for Charcot-Marie-Tooth (CMT) neuropathies. We have uncovered several pathological phenotypes that are shared among different CMT2 genotypes, which are exploited by SCREEN4PN.

Methods:
To evaluate a potential treatment, SCREEN4PN uses iPSCs obtained from CMT2 patients with different genotypes, two control lines, and one isogenic line. These iPSCs are differentiated to motor neurons, and the potential treatment is applied. The effect of the treatment is readout using several methods based on the shared pathological phenotypes, including but not limited to organelle transport assays (mitochondria, lysosomes), metabolic assays (oxygen consumption rate), neurite network measurements, and several protein biomarkers.

Results:
The SCREEN4PN platform was able to evaluate a compound in about 20% of the time required to do the same in a mouse model. So far, we have tested several compounds, and completed one study. In 2023, we aim to service two more studies in collaboration with companies. We will present the workflow and possibilities of the platform.

Conclusions:
Due to the low time and cost needed to evaluate a compound using SCREEN4PN in comparison to mouse models, the platform can benefit pharmaceutical industries, clinical research organisations, and academic partners. To facilitate research into CMT1 and other neuromuscular diseases, we are working on expanding the platform with more standardized assays, and different models, such as neuromuscular organoids (NMOs).

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Yes

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Grant Support:

Keywords: Charcot-Marie-Tooth disease, Compound validation, iPSC, Motor Neurons, Organoids

Genetic modifiers in hereditary and acquired TTR amyloidosis: update on genome-wide association study

Poster No:
P 186

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Introduction:
The recent discovery of disease modifying therapies has changed the natural history of hereditary transthyretin (ATTRv) amyloidosis from an invariably lethal to a treatable condition. However, we still lack effective biomarkers to define and predict the disease onset. Indeed, ATTRv amyloidosis is clinically heterogeneous both across countries and families and the basis of this variability cannot be entirely explained by the specific mutation in the TTR gene. Also, factors favoring wild-type TTR deposition are still largely unknown. Therefore, a role for genetic modifiers has been suggested for these two conditions. The aims of the study are: 1) to perform a genome-wide association (GWA) analysis to identify loci harboring genetic variations that modify age of onset, penetrance, phenotype, and severity 2) to characterise by long-read sequencing TTR-containing region and GWAS loci

Methods:
1) To perform a GWAS by InfiniumTM Global Screening Array-24 v3.0 (Illumina) with additional custom content on a discovery cohort of Val30Met ATTRv patients looking at genetic modifiers of AOO, penetrance, phenotype, and severity. Patients affected by ATTRwt amyloidosis will be also tested in a complementary case-control GWAS 2) To perform long-read sequencing (Oxford Nanopore) of TTR-containing region and GWAS loci in ATTRv patients with peculiar phenotypes

Results:
To date, n=33 Centres across the globe have been included and local ethic approval has been obtained by all participating Centres. First GWAS results from n=1000 ATTRv patients are expected in spring 2023. Targeted long-read sequencing (Oxford Nanopore) has been optimized to accurately detect the haplotype entailing TTR gene and measure satellite length in the genomic region.

Conclusions:
The proposed research will hopefully lead to the identification of novel genetic risk factors, informing disease prognosis and guiding monitoring and treatment. Also, it will provide seminal information about the mechanisms involved in amyloid deposition, potentially leading to the identification of novel drug targets.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: TTR, Genetic modifiers, Amyloidosis, Age of onset, Genome-wide association study

Knockout Of Proteasome Activator 200 (PA200) Rescues Neuropathy In The S63del Mouse Model Of Charcot Marie Tooth 1B

Poster No:
P 187

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Introduction:
In the S63del mouse model of CMT1B, and in models of other diseases caused by the expression of mutant, aggregation-prone proteins, there is a decrease in the 26S proteasome's ability to degrade proteins. The resulting insufficient protein breakdown causes an accumulation of un-degraded, potentially toxic proteins that contributes to disease progression. The cellular response to a decrease in proteasomal protein degradation has been best studied with pharmacological proteasome inhibitors, which induce in all cells an upregulation of proteasome subunits and of one of the four alternative activators of the proteasome: PA200. In S63del mice, proteasome subunits and PA200 are also upregulated in the affected sciatic nerves.

Methods:
To test genetically whether the upregulation of PA200 in S63del is an adaptive response to 26S proteasome impairment, we generated S63del//PA200-/- mice and evaluated proteostasis and nerve pathology.

Results:
Surprisingly, the ablation of PA200 in S63del increased proteasome activity and protein degradation in the sciatic nerves, apparently by increasing the amount of assembled, active 26S proteasomes. These effects were not seen in PA200-/- mice and thus, were specific to the neuropathic conditions. S63del//PA200-/- mice had less accumulation than S63del of misfolded proteins and, accordingly, less of an Unfolded Protein Response. Furthermore, in the sciatic nerves of S63del//PA200-/- mice, myelin thickness and nerve conduction were restored to WT levels.

Conclusions:
The upregulation of PA200 is maladaptive in S63del and its genetic ablation prevented the onset of the neuropathy. Activating proteasomal protein degradation is a new approach to treat diseases in which the proteasome is impaired. Pharmacologically promoting PKG-mediated phosphorylation of the 26S proteasome was recently reported to restore proteostasis, myelin thickness, and nerve conduction in S63del mice. Reducing PA200 could be a new genetic approach. PA200 ablation had little to no measured effect in WT mice, making it a promising candidate for gene silencing in CMT1B neuropathy.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: CMT, Proteasome, Proteostasis, UPR, PA200

Testing Race, Ethnicity and Gender Identities with Expanded Demographic Categories for Capturing the True Diversity

Poster No:
P 188

Authors:
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Introduction:
The Inherited Neuropathy Consortium (INC) currently categorizes race and ethnicity of patients using the National Institute of Health's (NIH) standardized race categories: American Indian or Alaska Native, Asian, Black, or African American, Native Hawaiian or Other Pacific Islander, and White and for ethnicity selecting Hispanic, Latino, or Spanish origin or Not Hispanic, Latino, or Spanish origin. The NIH's categories for gender are Male, Female, and Unknown or not reported. The NIH's categories for sex are not available. Our aim is to capture the true diversity and promote inclusion of all individuals with rare diseases who have joined the RDCRN.

Methods:
For the first phase of this project, we created an updated demographics form that was piloted at three of our study sites for three months in 2022. The form contained an expanded version of the NIH's race, ethnicity, and gender/sex identity categories. For the second phase of this project, this demographics form has been turned into a survey for distribution to all registrants of the Rare Disease Clinical Research Network (RDCRN) Contact Registry.

Results:
The expanded demographic pilot showed notable changes to the racial makeup of enrolled participants when compared with the NIH's current categories. 78.6% of enrolled subjects identify as 'white' according to the NIH's current categories, but the data collected showed a decrease to 66.7%. The 'other' race category decreased from 9.5% to 0%, while the 'mixed' category changed from 4.5% to 23.8%. In the second phase of this project, our team will compare the standard NIH recommended categories that survey participants had initially selected when signing up for the RDCRN contact registry to the demographic data collected when completing the updated survey.

Conclusions:
We expect to determine whether expanding gender, sex, race, and ethnicity categories enables us to capture a greater amount of diversity in our patients' demographics report.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: The Inherited Neuropathy Consortium is part of the NIH Rare Diseases Clinical Research Network (grant #1U54NS065712-01)

Keywords: Rare Genetic Population, Demographics , RDCRN, INC, Contact Registry

Diversity initiative on performing standardized Virtual Charcot-Marie-Tooth Exam Score (vCMTES) in Spanish-Speaking Countries

Poster No:
P 189

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Institutions:
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Introduction:
The virtual Charcot Marie Tooth Exam Score (vCMTES) is a composite score, based on the CMT Exam Score (CMTES) that combines questions about a patient's daily function with items on the neurological examination. This outcome measure provides a model to outreach patients who are dominant in a language other than English such as Spanish. We have reached out to enroll patients who are outside of the United States and who are Spanish-dominant from Mexico, Spain, and Columbia.

Methods:
The vCMTES was performed virtually with the examiner using a Zoom or similar format and the language interpreter to translate to/for the patient and examiner. The vCMTES differs from CMTES in that light touch and position sense replace pinprick and vibratory sensation, respectively. The remote INC examiner provides the first few vCMTES questions for the Spanish interpreter to translate the examination. Parts of the exam are performed by a family member or caregiver while the examiner is observing. After 2-4 weeks, a re-test was performed to test the reproducibility of the evaluation.

Results:
10 Spanish-speaking patients with genetically defined CMT were examined remotely and scored based on the vCMTES, five of whom completed the retest visit. Patient impairment ranged from mild (vCMTES of 5) to severe (vCMTES of 26). Patients with CMT1A, CMT2A, CMT2F, CMT2K, and CMT2M were included. Re-test scores were highly reproducible. In addition, each patient completed a survey questionnaire providing feedback on their experience, which was uniformly positive. An additional benefit was enabling several participants to identify local resources at the Charcot-Marie-Tooth Association center of excellence in Guadalajara, Mexico.

Conclusions:
The vCMTES was easily translatable into Spanish enabling evaluation of patients who could not have been evaluated at CMT clinics or by English-speaking examiners. We are now further extending our remote evaluations to non-English speaking patients with Italian, Portuguese, Turkish, and Hindi.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: Inherited Neuropathy Consortium is part of the NIH Rare Diseases Clinical Research Network (grant #1U54NS065712-01)

Keywords: Virtual CMTES, Spanish Language , Spanish Countries

Statistical Shape Modeling of Modified Plaster Casts in Ankle-foot Orthoses Production

Poster No:
P 190

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Introduction:
Ankle foot orthoses (AFOs) are prescribed to children with Charcot-Marie-Tooth disease (CMT) to improve walking ability, reduce falls from foot drop, and maintain body posture. The traditional manufacturing of custom AFOs involves plaster molding, cast modification, thermal vacuum forming and personal fitting. The shape of the modified plaster cast determines the basic shape of the AFO and is essential for fit and functionality, however the quantification of this process is lacking. The aim of this study was to develop statistical shape models (SSMs) to uncover the shape variability of the modified plaster casts to improve AFO production for children with CMT.

Methods:
Modified casts of children prescribed AFOs (n=78) were captured using 3D scanning. An established method using open-source package GIAS2 was employed to generate the average post-modified cast shape and 3D shapes of the ±2 standard deviations along the first three principal components (PCs). Ten cast morphometric measurements were analyzed on the generated post-modified casts of the PCs.

Results:
The average post-modified plaster cast of the cohort demonstrated a smooth boot-like shape. The first three PCs covered 95% of the shape variation, revealing that the modified casts predominately varied according to the overall size (volume), forefoot-rearfoot alignment and rearfoot valgus angle.

Conclusions:
Plaster casts were modified with a combination of common features and deformity-specific changes. The findings provide insight into managing, evaluating, and improving the plaster modification process of traditional AFO production, which can also assist in digital fabrication to enhance the delivery of the AFO devices for children with CMT.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Ankle Foot Orthosis (AFO), Orthotics, CMT, AFO manufacturing , Plaster cast modification

Using Wearable Sensors To Derive Gait Metrics In Charcot-Marie-Tooth Type 1A Participants: A Pilot Study

Poster No:
P 191

Authors:
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Introduction:
Individuals with Charcot-Marie-Tooth type 1A (CMT1A) display slowly progressive weakness and sensory loss leading to functional limitations of gait. Preclinical therapeutic advances have led to the development of potential treatments for CMT1A, emphasizing the need for clinical trial readiness. The purpose of this study was to determine if wearable sensors could be used to assess gait in individuals with CMT1A for future trials.

Methods:
Adults with CMT1A and healthy controls were recruited for this 12-month study. Participants wore three adhesive sensors, for 24-hours, to gather quantitative gait data during in-clinic assessments and within the natural environment. Gait metrics were derived from raw data using disease-specific algorithms. Group differences for gait metrics were analyzed using Mann Whitney U tests. Correlation analyses were used to assess relationships between the metrics and clinical outcome measures, more specifically the CMT-Functional Outcome Measure (CMT-FOM).

Results:
30 participants were enrolled, 15 CMT1A and 15 controls. Group differences during in-clinic assessments showed longer step durations (median-CMT1A=0.51 seconds/step; median-control=0.45 seconds/step; $p<0.001$), shorter step lengths (median-CMT1A=0.73 meters; median-control=0.74 meters; $p=0.03$), and slower gait speeds (median-CMT1A=1.37 meters/second, median-control=1.62 meters/second; $p<0.001$) for CMT1A participants. Similar significant trends were noted between groups within the natural environment. Comparing in-clinic assessments with natural environment data, both groups demonstrated shorter step durations, longer step lengths, and faster gait speeds while in-clinic. Moderate, negative correlations were found between CMT-FOM and step length (in-clinic: $r=-0.59$, $p=0.02$; natural environment: $r=-0.57$, $p=0.04$;), and gait speed (in-clinic: $r=-0.64$, $p=0.01$; natural environment: $r=-0.66$, $p=0.02$).

Conclusions:
Wearable sensors are feasible for use in individuals with CMT1A to gather both in-clinic and natural environment gait data. This method of generating gait information may prove useful for early-phase clinical trials; however, larger longitudinal studies are needed to confirm these findings and evaluate the responsiveness of these wearable sensors.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: Charcot-Marie-Tooth Association

Keywords: Wearable sensors, Outcome measures, Gait, Charcot-Marie-Tooth type 1A

An atlas of tandem repeat sizes and motif composition in RFC1 and over 1 million other loci in more than 1,000 long-read genomes

Poster No:
P 192

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Introduction:
Repeat expansions in DNA are the cause of over 40 neurological disorders, and have been found in cases of peripheral neuropathy, such as NOTCH2NLC, ATXN2, ATXN3, and RFC1. However, limitations in short-read genomic sequencing have contributed to a potential barrier of discovery, in a field that is already seldomly studied.

Methods:
Through the All Of Us research program we used a new long-read tandem repeat genotyping tool, TRGT, to characterize over 1 million repetitive loci in each of more than 1000 long-read genomes.

Results:
We analyzed the RFC1 locus in this healthy cohort to help understand how repeat length and motif composition are distributed in the population. We can use this information to better delineate RFC1 pathogenic thresholds and motif conformations. However, we also compared the long-read genotyping to corresponding short read data, which will greatly aid studies that rely on short-read data. We have cataloged the tandem repeat size distribution of our cohort.

Conclusions:
This database will assist in future discovery of more neuropathy-causing repeat expansion disorders, provide greater resolution of current peripheral neuropathy-causing repeats such as in RFC1.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Repeat Expansion, RFC1, Bioinformatics

Pre-clinical studies in induced Pluripotent Stem Cell (iPSC) lines with SORD mutations linked to a recessive neuropathy

Poster No:
P 193

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Introduction:
Biallelic mutations in the gene coding for sorbitol dehydrogenase (SORD) are associated with a common form of recessive inherited neuropathy. To model this CMT type, we generated induced-Pluripotent Stem Cells (iPSCs) from patients with the SORD neuropathy and differentiated them into spinal cord motor neurons. We are expanding on previous studies to further elucidate disease specific phenotypes and the effects of small molecule therapies.

Methods:
Motor neurons were differentiated using a previously published protocol. Sorbitol levels were measured by mass spectrometry. Neurofilament Light Chain content was measured by ELISA and normalized to cell count. Mitochondria staining was done using MitoTracker Green FM.

Results:
Previously, our lab had generated iPSC lines from 3 different patients and have generated lower motor neurons to model disease. To assess an important disease phenotype, we measured intracellular sorbitol levels via mass spectrometry. We confirmed that the SORD neurons have increased sorbitol compared to controls. We then looked at supernatant Neurofilament Light Chain (NFL) as an indicator of neurodegeneration. SORD neurons trend towards increased supernatant NFL. We expanded our investigation to observe possible mitochondria phenotypes. Looking at mitochondria size, we saw that the SORD mitochondria was significantly decreased in size compared to healthy controls. We also saw exposure to sorbitol in the media caused the signal intensity to increase, indicating possible membrane potential changes. Future work involves studying mitochondrial trafficking and respiration as well as testing small molecule inhibitors to reverse disease phenotypes.

Conclusions:
SORD motor neurons replicate disease phenotype with elevated intracellular sorbitol levels. They also trend towards having an elevated level of supernatant NFL, indicative of a neurodegenerative phenotype. We observed that the SORD mitochondria show a decrease in size and that mitochondrial membrane potential may be influenced by environmental sorbitol. Future experiments involve using small molecule inhibitors to reverse phenotypes and expanding on current mitochondrial studies.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Charcot-Marie-Tooth Disease, Motor Neuron, SORD, Neuropathy, iPSC

P62/sequestosome-1 as a severity-reflecting plasma biomarker in Charcot-Marie-Tooth disease type 1A

Poster No:
P 195

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Introduction:
Recent studies have demonstrated that autolysosomal dysfunction leads to secretion of autophagy machineries, including autophagy receptors such as p62/sequestosome-1 (p62), via exosomes. We tried to determine the elevation of plasma p62 protein levels in patients with inherited demyelinating peripheral neuropathy, Charcot-Marie-Tooth disease 1A (CMT1A), in which autophagy is suppressed in myelinating Schwann cells.

Methods:
We collected blood samples from 69 CMT1A patients and 59 healthy controls. Plasma concentrations of p62 were analysed by ELISA, and compared with CMT neuropathy score version 2. A mouse model of CMT1A (C22 mouse) was used to determine the source and mechanism of plasma p62 elevation.

Results:
Plasma p62 was detected in healthy controls in ELISA, but the levels were significantly elevated in CMT1A patients compared to controls. The elevated plasma p62 levels were correlated with CMT neuropathy score version 2 ($r = 0.621$, $p < 0.0001$) and disease duration ($r = 0.364$, $p < 0.01$) in CMT1A patients. In a mouse CMT1A model, increased p62 expression was observed not only in pathologic Schwann cells but also in plasma.

Conclusions:
Our findings indicate that plasma p62 measurement could be a valuable tool for evaluating severity and Schwann cell pathology in CMT1A patients.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Charcot Marie Tooth disease

Genetic Features of Inherited Peripheral Neuropathy in a Japanese Cohort

Poster No:
P 196

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Introduction:
Inherited peripheral neuropathy (IPN), represented by the most common form, Charcot-Marie-Tooth disease (CMT), is a group of genetically heterogeneous neurological diseases characterized by peripheral nervous system involvement. Genetic diagnosis of IPN/CMT is always difficult, and aim of this study is to elucidate the genetic features of patients with IPN/CMT in Japan.

Methods:
From April 2007 to July 2022, a total of 2780 cases clinically diagnosed with IPN/CMT were collected from all over Japan, and the cases with *PMP22* duplication/deletion mutations were pre-excluded. Genetic analyses were performed using gene-panel sequencing (DNA microarray/next-generation sequencing), whole-exome sequencing, copy number variant analysis, and repeat expansion analyses for *RFC1* and *NOTCH2NLC* genes.

Results:
Among 2780 cases, we identified pathogenic/likely pathogenic variants within 959 cases, yielding a diagnostic rate of 34.5%. The top-ranking genes were *MFN2*, *GJB1*, *MPZ*, and *MME*. Within varied onset age groups, *MFN2* was the most common causative gene in cases with onset age <= 20 years, while *GJB1* and *MPZ* were the major causes of cases with onset age between 21~40 years and >= 41 years, respectively. On the other hand, *GJB1* was the main gene associated with the demyelinating type IPN/CMT, and *MFN2* was the main reason accounting for the axonal type. Furthermore, we also identified *MPZ* duplication (1 case), *GJB1* gene deletions (2 cases), multi-type *RFC1* repeat expansions (18 cases), and *NOTCH2NLC* repeat expansions (23 cases).

Conclusions:
Our comprehensive genetic analyses enable us to delineate the genetic spectrum in this Japanese nationwide cohort of IPN/CMT patients, and may aid in the development of more efficient genetic screening strategies. Necessity of copy number and repeat expansion analyses are underlined to improve the molecular diagnostic rate.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: This work was supported by Grants-in-Aid from the Research Committee of Ataxia, Health Labour Sciences Research Grant, the Ministry of Health, Labour and Welfare, Japan (20317603, 201610002B). This research was also supported by the Research program for c

Keywords: CMT

Functional Validation of *DNMT1* Variants Detected by Next Generation Sequencing

Poster No:
P 197

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Introduction:
DNMT1, encoding DNA methyltransferase 1, was found associated with autosomal dominant cerebellar ataxia, deafness and narcolepsy, or hereditary sensory and autonomic neuropathy (HSAN) type IE, collectively referred as *DNMT1*-related disorders. Aim of this study is to assess the functional effect of variants detected in *DNMT1* gene, and demonstrate their genotype-phenotype correlations.

Methods:
DNA samples were collected from patients with inherited neurological diseases, consisting of hereditary sensory and autonomic neuropathy (HSAN), spinocerebellar ataxia (SCA), and Charcot-Marie-Tooth disease (CMT). Gene-panel sequencing targeting 18 HSAN-related genes, and whole-exome sequencing were performed. Detected *DNMT1* variants were introduced into cDNA plasmid by site-directed mutagenesis, and were then transfected into HEK293T cells. Recombinant DNMT1 protein was isolated, and tested using a DNMT activity assay kit.

Results:
DNMT1 variants were identified from six patients with clinical diagnosis of HSAN (3 cases), SCA (2 cases), and CMT (1 case), using either gene-panel or whole-exome sequencing. The variants were p.E338del, p.Y511H, p.Y540C, p.H569R, p.A1334V, and p.P1546S. Despite cerebellar ataxia was the major symptom of two SCA patients, all patients presented with sensory predominant neuropathy except for the patient with p.E338del, who was clinically suspected with CMT. The other common symptoms were hearing loss (5/6) and cognitive disorder/cerebral atrophy (5/6). Functional assay of wild-type and mutant DNMT1 proteins revealed significant reduction of methylation activity from all mutant proteins apart from p.E338del.

Conclusions:
Reduced methylation activity of five mutants, distributing within/closely downstream of the replication foci domain or site-specific DNA-cytosine methylase domain of DNMT1, suggesting a loss-of-function effect. In comparison, p.E338del, locating upstream of the replication foci domain, is more likely benign. This study extends the clinical and mutational spectrum of *DNMT1*-related disorders, and sheds light on understanding of the genotype-phenotype correlation.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: This work was supported by Grants-in-Aid from the Research Committee of Ataxia, Health Labour Sciences Research Grant, the Ministry of Health, Labour and Welfare, Japan (20317603, 201610002B). This research was also supported by the Research program for c

Keywords: DNMT1, Next generation sequencing, Hereditary sensory and autonomic neuropathy, Charcot-Marie-Tooth disease, Spinocerebellar ataxia

Investigating the SNPs involoved in metabolism of Cypriot ATTR patients

Poster No:
P 198

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Introduction:
ATTR is a rare disease with autosomal dominant inheritance, it results from mutations in the transthyretin gene. The predominant mutation in the Cypriot population is the Val30Met mutation caused by substituting Valine for Methionine in position 30. The aim of this project was to investigate metabolic involvement in carriers and patients of the V30M mutation, with varying symptoms and age of onset. The SNPs (IRS1), (FTO), (HNFIA) and (MC4R) wereinvestigated.

Methods:
Demographic data was previously collected from ATTR patients' at the Cyprus Institute of Neurology and Genetics. The data assessed included i) gender and ii) age. The Mann-Whitney Test was used to obtain the p-value for age. The gender of individuals' is provided by frequency. The SNPs investigated were, SNP A (HNF1A), SNP B (FTO), SNP C (MC4R), and SNP D (IRS1). DNA samples from a cohort of 48 patients and 48 gender/age-matched controls were used for TaqMan SNP Genotyping Assay. PCR purification was performed through a MontageTM PCRm96 plate. The ABI PRISM di-Deoxy Terminator Cycle sequencing kit v 3.1 was used. Statistical analysis was performed using R. The Pearson's chi-square test was performed to determine a statistically significant difference between cases vs controls for IRS1, FTO, HNF1A and MC4R.

Results:
The mean age of the case and control groups was 48.7 and 49.85 years respectively, However, no significant p-value was obtained between cases and controls as both groups had 52% (25) females and 48% (23) males. Regarding, SNP A (HNF1A) (p-value 1), SNP B (FTO) (p-value 0,663) and SNP D (IRS1) (p-value 0,412) were not statistically significant. However, SNP C (MC4R) (p-value 0,000988) was statistically significant.

Conclusions:
To the best of our knowledge, this is the first study investigating the SNPs of HNF1A, FTO, MC4R and IRS1 involved in metabolism of Cypriot ATTR patients. Our study found that SNP C (MC4R) was strongly related to ATTR.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: ATTR, SNPs , SNP metabolism, MC4R

Recessive NEFL mutation associated with early onset complicated hereditary spastic paraparesis phenotype

Poster No:
P 199

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Introduction:
Mutations in the NEFL gene underlies Charcot Marie Tooth disease, either the demyelinating CMT1F or the axonal CMT2E form. Most of the pathogenic NEFL mutations are dominantly inherited missense mutations functioning through a gain of function mechanism. All reported autosomal recessive NEFL mutations have been homozygous non-sense variants. Herein we report a novel phenotype associated with recessive NEFL mutation.

Methods:
Medical record was reviewed. The following was characterized for the patient: age of onset of motor symptoms, genetic mutation, inheritance pattern, clinical features, electromyography and nerve conduction studies (EMG/NCS) results, and brain MRI findings.

Results:
The patient was noted stiffness and tremor of his legs at birth. Developmental concern was raised when he was 6 months old. He was evaluated because of delay in ambulation and was found to have spastic diplegia. His arms were thought to be find and parents did not have concern for his social development. He had a normal brain MRI and full spine MRI. whole exome sequencing performed when the was 2 years old identified homozygous variant c417C>G; pY139X in the NEFL gene, due to parental UPD from father. At 31 months of age, his neurological examination showed normal cranial nerves exam, normal muscle tone and strength in arms, and spasticity of both legs with pathologically brisk reflexes at the knees and ankle clonus, with upgoing toes. NCS and EMG at 2.5 years of age showed absent sensory responses in arm and leg. Compound motor action potentials were reduced/absent in peroneal, posterior tibial, median and ulnar motor responses, with uniform slowing to 16-24 m/s.

Conclusions:
Our patient with homozygous mutation of the NEFL gene has a complicated hereditary spastic paraparesis phenotype. Our report has expanded the genotype and phenotype of recessive NEFL mutations.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: recessive NEFL, complicated HSP

Deep phenotyping of neuropathy associated with biallelic NMNAT2 variants

Poster No:
P 200

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Introduction:
Studies suggest that defects in NMNAT2 could predispose an individual to develop neurodegenerative disease; however, there was little direct evidence connecting mutations in the genes involved in axon degeneration to human neurological disease. We recently reported biallelic NMNAT2 variants identified in 2 siblings with severe neuropathy. A mouse model harboring the Nmnat2V98M/R232Q mutations identified in the siblings recapitulated the cardinal symptoms of the human disease, confirming the association of NMNAT2 mutations and inherited neuropathy in human (Dingwall et al, JCI 2022). Herein detail phenotypes of the sibling are described.

Methods:
Medical records were reviewed. The following was characterized: age of onset of motor symptoms, clinical features, genetic mutation, inheritance pattern, electromyography and serial nerve conduction studies (EMG/NCS) results, and other relevant tests.

Results:
Patients 1 and 2 are brothers from nonconsanguineous, healthy parents of African American ancestry. Both were born following an uneventful pregnancy. Both had normal early development but experienced an episode of acute hypotonia, weakness, and respiratory failure that required mechanical ventilation at the age of 13 months and 11 months, respectively. Nerve conduction studies and electromyography at the time of symptom onset showed features of sensory, and motor neuropathy with some multifocal features thought to be consistent with Guillain-Barré syndrome. After treatment with intravenous immune globulin, they were taken off ventilatory support but exhibited residual weakness. Both had almost identical clinical features that are characterized by baseline weakness with episodic attacks frequently triggered by an infectious process. Whole-exome sequencing performed on the brothers and their parents identified compound heterozygous variants (c. 695G>A [p.Arg232Gln] and c.292G>A [p.Val98Met]; R232Q and V98M, respectively) in NMNAT2 in both siblings. Here, their clinical symptoms, clinic course and serial NCS and EMG findings are presented.

Conclusions:
NMNAT2 mutations lead to severe neuropathy with relapsing features in human.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: NMNAT2 variants, neuropathy

Molecular Imaging Study of the Immune Response in Muscle Denervation: a High-Tech Study in a Murine Model of CMT1B

Poster No:
P 201

Authors:
Federico Zaottini[1,2], Roberta Resaz[3], Riccardo Picasso[4,2], Mattia Camera[5], Marina Grandis[6,2], Simonetta Astigiano[3], Laura Emionite[3], Vanessa Cossu[3], Gianmario Sambuceti[4,2], Cecilia Marini[7,2], Mehrnaz Hamedani[8], Angelo Schenone[6,2], Carlo Martinoli[1,2], Lucilla Nobbio[5,2]

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Introduction:
We recently generated a mouse model carrying the MPZD61N mutation, causing in humans a severe early onset form of CMT1B (Veneri et al, 2022). Previous studies described a potential role of innate immunity in the pathogenesis of neuropathy in CMT animal models. Molecular imaging has proved to be a valuable non-invasive mean to explore the development and trend of micro-inflammatory processes in vivo. In the present study, we aim at: i) verifying the presence of immune/inflammatory cells infiltration in nerve and muscle of this novel CMT1B mouse model by molecular imaging techniques and histopathology ii) correlating the imaging findings and the entity of immune/inflammatory cells infiltrate with disease phenotypes.

Methods:
WildType, heterozygous and homozygous CMT1B mice were subjected to a sequential protocol including: i) evaluation of motor performance; ii) MRI in a dedicated 7 Tesla system, before and after administration of Ultrasmall Superparamagnetic Iron Oxide contrast agents, aiming to label the macrophages; iii) whole-body micro-PET using a tracer targeting transporter protein TPSO (a marker of inflammatory cells). Then, animals were sacrificed, sciatic nerves and different muscles of the paws collected for histochemical analysis to detect inflammation and evaluate muscle atrophy.

Results:
We found an increased density of inflammatory cells in mutant mice both heterozygous and homozygous compared with the WT littermates. Functional MRI parameters indicate a higher degree of nerve alterations in the mice with the highest inflammatory infiltrate. At micro-PET, an increased tracer uptake in distal hind limbs was found, as a potential indicator of inflammatory infiltrates in denervated muscles.

Conclusions:
Even if this study represents a pilot investigation of inflammatory response in muscle and nerve in this severe form of CMT1B neuropathy, our results display that low-grade inflammation influences molecular imaging parameters and may contribute to the neuropathic phenotype.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: CMT1B, MRI, micro-PET, Ultrasound, Immunity

Prevalence estimation of ATTRv amyloidosis in China based on genetic databases

Poster No:
P 202

Authors:
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Introduction:
Amyloid transthyretin (ATTR) is divided into either hereditary (ATTRv) or sporadic (ATTRwt) and ATTRv is a rare hereditary disease transmitted as an autosomal dominant manner. Its global prevalence is traditionally estimated as 5,000 to 10,000 persons. However, it may be underestimated and the exact prevalence of ATTRv in China mainland remains unknown.

Methods:
The Genome Aggregation database (gnomAD) database and two genomic sequencing databases -- China Metabolic Analytics Project (ChinaMAP) and Amcarelab gene database, were integrated to estimate the prevalence of ATTRv in the world and mainland Chinese populations. Pathogenic variants allele frequency and the prevalence of ATTRv was calculated.

Results:
Six variants, including 470 alleles, were defined as pathogenic variants in gnomAD. The prevalence of ATTRv in the world population was 57.4/100,000. Two variants (2 allele counts) and 15 variants (34 individuals) were defined as pathogenic variants in the ChinaMAP database and the Amcarelab exome database, respectively. Thus, the estimated prevalence interval of ATTRv in mainland China was 18.9/100,000-74,9/100,000.

Conclusions:
The present study demonstrated that the previous prevalence was greatly underestimated using traditional methods. Therefore, raising awareness of the disease is essential for recognizing ATTRv in its early stage

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Amyloid transthyretin, Prevalence;

The Clinical Significance of Nerve Axonal Excitability in Amyotrophic Lateral Sclerosis

Poster No:
P 203

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Introduction:
This study applied a threshold tracking technique to assess changes in ALS axonal excitability and its correlation with neuronal degeneration.

Methods:
The ALS patients meeting the modified El Escorial diagnostic criteria were recruited. Healthy volunteers were also included as normal control group. Clinical characteristics of 47 ALS patients were recorded, and electromyography as well as threshold tracking examinations were performed. Comparison between two groups were performed using independent sample t-test and correlation analysis with pearson.

Results:
Strength duration time constant (SDTC) was increased in 47 ALS patients, suggesting an upregulation of persistent Na channel function. The threshold electrotonus of TED40 and TED90 were significantly increased in the ALS group, suggesting potassium channel dysfunction in the internodal. Greater super-excitability in ALS, which also suggested fast potassium channel dysfunction. The median SDTC, TED40 and TED90 increased before clinical sign in the upper limbs. Regression analyses showed TED40 and SDTC increased with disease progression rate (TED40: P=0.02, SDTC: P=0.03).

Conclusions:
According to the results of threshold tracking, ALS patients present persistent sodium channel upregulation, potassium channel dysfunction, and increased nerve excitability. Sodium and potassium channel dysfunction precede clinical symptoms and conventional electrophysiological abnormalities, which are early electrophysiological indicators of ALS. Moreover, this study found that function of sodium and potassium channel was correlated with disease progression rate and maybe the factor of poor prognosis.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: amyotrophic lateral sclerosis, nerve axonal excitability, electrophysiology test, ion channel

Axonal excitability in spinal muscular atrophy caused by DYNC1H1 gene mutation

Poster No:
P 204

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Introduction:
DYNCIH1 SMA is autosomal dominant, also known as SMA-LEG.Neural axon excitability can detect the membrane potential level and various ion channel functions of nerve axons in vivo, also known as threshold tracking (Qtrack). Therefore, in this study, Qtrack technology was applied to investigate the nerve excitability changes in SMA patients and mice with DYNCIH1 mutation， and to explore the possible pathophysiology.

Methods:
3 SMA-LEG patients and 10 age-sex-matched healthy volunteers were involved in this study. The mouse experimental group was 5 DYNC1H1F580Y-Loa mice cultured using sperm haploid embryonic stem cell technology, and the test control group was five littermate wild-type mice including the behavior test, electrophysiology test and Qtrack. Spinal cord anterior horn cell count and sciatic nerve pathology examination were also tested.

Results:
The strength duration time constant (SDTC) of the median nerve in 3 SMA-LEG patients was 0.598ms,1.59ms,0.469ms, which was significantly longer than the normal control (0.41±0.02ms). The 4-week and 12-week Loa mice lost weight more than the normal controls, and all DYNC1H1 mice had leg-hugging movements and showing significant differences in the maximum grip. The tail nerve motor amplitude of 4 weeks and 12 weeks loa mice was significantly lower than wild-type mice. The mean SDTC of 4-week loa mice was 0.34±0.02ms, and the SDTC of 12-week loa mice was 0.43 ± 0.08, significantly prolonged compared with wild type (0.19±0.03ms). No significant abnormalities were found in spinal anterior horn cell count and sciatic nerve pathology in 4-and 12-week loa mice.

Conclusions:
The present study found that the excitability examination of SMA-LEG patients and DYNCIH1F580-Loa mice showed prolonged SDTC, suggesting increased NaVp influx. In addition, this study confirmed that abnormal neural excitability appeared before the appearance of abnormal anterior horn cell count and sciatic nerve pathology, so that sodium upregulation may be an upstream factor in the pathogenesis of motor neurons and their axonal degeneration.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: National and Provincial Multi-disciplinary Cooperation in Diagnosis and Treatment of Major Diseases Capacity Improvement Project (Shanghai Municipal Health Commission) and Shanghai Municipal Science and Technology Major Project (No. 2017SHZDZX01), and Sha

Keywords: Axonal excitability, spinal muscular atrophy, DYNC1H1 gene mutation

Diversity, Equity, and Inclusion initiative on performing standardized Virtual Charcot-Marie-Tooth Exam Score (vCMTES) in Italian-Speaking Countries

Poster No:
P 205

Authors:
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Introduction:
The Inherited Neuropathy Consortium (INC) created a Diversity, Equity, and Inclusion (DEI) internship to provide an opportunity to address racial, ethnic, gender, and socioeconomic disparities in rare disease clinical research. The virtual CMTES (vCMTES) is a composite score, based on the CMT Exam Score (CMTES) that combines questions about patient's daily function with items on the neurological examination This outcome measure provides a model to outreach patients who are dominant in a language other than English such as Italian. We have reached out to enroll Italian speaking patients who are non-English speakers from Italy.

Methods:
The vCMTES was performed virtually with the examiner using a Zoom or similar format. The vCMTES differs from CMTES in that light touch and position sense replace pin prick and vibratory sensation. The remote INC examiner provides the instructions and the examination is performed by a family member or caregiver while the examiner is observing. After 2-4weeks, a re-test was performed to test the reproducibility of the evaluation.

Results:
10 Italian- speaking patients (7 Females and 3 Males) with CMT were examined remotely and scored based on the vCMTES, three of whom also completed the retest visit. Patient impairment ranged from mild (vCMTES of 3) to severe (vCMTES 24). 3 Patients with CMT1A, 2 with CMT1E, 1 with CMT2 and 4 with CMTX1, mean age 36 yrs (range 20-58) were included. Test-retest scores were highly reproducible. In addition, each patient completed a survey questionnaire providing feedback on their experience, which was uniformly positive.

Conclusions:
The vCMTES was easily translatable into Italian enabling evaluation of patients who could not have been evaluated at CMT clinics. We are now further extending our remote evaluations of non-English speaking patients with Spanish, Portuguese, Turkish and Hindi.

References:
No

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References 2:

References 3:

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Grant Support: grant #1U54NS065712-01

Keywords: CMT, Outcome Measures, Remotly Outcome Measures, Charcot Marie Tooth, Assessment

Respiratory updates in CANVAS

Poster No:
P 206

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Introduction:
The phenotypic spectrum associated with biallelic RFC1 AAGGG repeat expansion includes Cerebellar Ataxia, with Neuropathy, and Vestibular Areflexia Syndrome (CANVAS). Moreover a chronic spasmodic dry cough is frequently also associated. Despite patients often report sleep disturbance, no data are found in the literature regarding the incidence of sleep breathing disorders in subjects affected by CANVAS.

Methods:
A respiratory evaluation protocol (CANVASleep) including the Epworth Sleepiness Scale (ESS), Fatigue Severity Scale (FSS), Force Vital Capacity (FVC), Polysomnography (PSG) was assessed to individuals diagnosed with CANVAS.

Results:
To date 10 CANVAS patients have been evaluated with the CANVASLeep: 5 F, 5 M, mean age 60 (range 47-73). The mean score of the ESS was 7.2 (range 3-10), of the FSS was 32 (range 19-46). The mean value of the FVC was 3.6 liters (89%) and the PSG showed 11.85 as mean value of the Apnoea-Hypopnoea Index (AHI) (range 5.7-18), associated with Cheyne-Stokes breathing in 4 individuals and for that reason the CPAP was introduced. All patients complained cough. The study is still ongoing.

Conclusions:
These are preliminary data from 10 patients and additional results will be included at the meeting. Results from this study will help to focus future studies to understand the impact of sleep-disordered breathing in CANVAS to better improve the management of individuals with CANVAS. Further, the results provide objective data that can be used in developing specific interventions which could improve the quality of life of patients.

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Yes

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Grant Support:

Keywords: CANVAS, Sleep Disorders, Cough, Polysomnography, Cerebellar Ataxia

International Diabetes Neuropathy Consortium

International Diabetes Neuropathy Consortium (IDNC) Abstracts

P 207 - 252

Sensitivity of clinical evaluation for discriminating small and large fiber diabetic neuropathy : a cross-sectional study

Poster No:
P 207

Authors:
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Introduction:
Routine clinical evaluation is usually considered sufficient for screening classical diabetic polyneuropathy (DPN) and the American Diabetes Association states that electrophysiological testing is not cost-effective. There is however a paradigm shift towards early diagnosis at the stage of reversible pure small fiber neuropathy (SFN). We therefore aim to investigate the sensitivity of clinical evaluation for discriminating small

Methods:
Patients were consecutively recruited from the cohort of the diabetic neuropathy clinic of Jordan Medical Services, Yaounde, Cameroon from February 2022 to January 2023. The Toronto Clinical Neuropathy Score and the SFN 2008 criteria were used for classifying Small and large fiber neuropathies. Electrochemical skin conductance (ESC) of hands and feet recorded by SUDOSCAN and Nerve Conduction studies (NCS) were used as reference for small and large fiber functions respectively.

Results:
A total of 71 patients were included (96% type 2, 2.7% glucose intolerance and 1.3% type 1). Mean age was 57.85± 10.79 with a Male/female sex ratio of 1.9:1. Mean HbA1c was 7.82±1.92. Based on clinical criteria, DPN was diagnosed in 80% of patients (large fiber 63.3% vs small fiber 36,7%). Mean ESC scores were. 60.07±14.57 and 61.27±12.93microsiemens for feet and hands respectively. The overall prevalence of DPN was 73.2% and that of pure SFN 25.3%. The level of agreement between clinical and electrophysiological diagnosis was poor (kappa = 0.3). Clinical evaluation correctly classified only 7 patients on 18 (38.9%) with SFN and 27 patients on 34 (79.4%) with large fiber dysfunction.

Conclusions:
Clinical evaluation has a low sensitivity of discriminating small and large fiber DPN. Simple paraclinical tools evaluating both small and large fibers shoud be included in routine assessment of diabetic patients for appropriate diagnosis and classification diabetic neuropathy.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: None

Keywords: Diabetic neuropathy, clinical evaluation,, small fiber neuropathy, , large fiber dysfunction

Sensitivity Of SUDOSCAN For The Diagnosis Of Carpal Tunnel Syndrome In Diabetes : a cross sectional study

Poster No:
P 208

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Introduction:
SUDOSCAN is an emerging tool for the effective screening of diabetic polyneuropathy (DPN). It measures electrochemical skin conductance (ESC) of both hands and feet. These values could be altered by other conditions. Carpal tunnel syndrome (CTS) is more frequent in diabetic patients compared to the general population. Reduced intraepidermal nerve fiber density have been reported in this condition. We sought to investigate the sensitivity of the SUDOSCAN for its diagnosis compared to nerve conduction Studies (NCS).

Methods:
Patients were consecutively recruited from the cohort of the diabetic neuropathy clinic of Jordan Medical Services, Yaoundé, Cameroon from February 2022 to January 2023. All participants underwent clinical evaluation. SUDOSCAN was used to measure hand ESC. Bilateral median nerve motor and sensory parameters were assessed with NCS. Diagnosis was made according to the criteria of the American Academy of Neurology.

Results:
A total of 71 participants with a mean age of 57.85±10.79 (96% type 2, 2.7% glucose intolerance and 1.3% type 1) were included. The Male/female sex ratio was 1.9:1. Mean HbA1c was 7.82±1.92. Mean ESC hand values in the total population was 61.27±12.93microsiemens. Considering a treshold of 50microsiemens, the proportion of pathologic hand scores was 16.9%. The prevalence CTS was 32.4% with 47.8% being asymptomatic. There was no agreement between hand ESC and Median NCS as indicated by kappa = -0.125. The sensitivity of Sudoscan for the diagnosis of CTS was 17.4% (4/23), and the specificity 70.8% (34/48). The negative predictive value (NPV) was 64.2% (34/53) and the positive predictive value (PPV) 22.2% (4/18).

Conclusions:
SUDOSCAN has a low sensitivity and positive predictive value for the diagnosis of CTS in diabetic patients. Pathologic hand ESC values should orientate the clinician more towards diabetic neuropathy rather than alternate diagnosis.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: None

Keywords: SUDOSCAN, Carpal Tunnel Syndrome, , Diabetes

Mislabeling of skin biopsy specimens: A retrospective investigation into potential errors in diagnosis of non-length dependent small fiber neuropathy

Poster No:
P 209

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Introduction:
We have observed clinical cases of 'biopsy-proven' non-length dependent small fiber neuropathy (NLD-SFN) many of which have non-specific symptoms, normal neurological examination and normal repeat skin biopsies. Some of these cases have a reversal of the proximal to distal intra-epidermal nerve fiber density (IENFD) gradient. We hypothesize that specimen mislabeling is one possible explanation. Objective: To investigate the frequency of skin biopsy specimen mislabeling as a cause for misdiagnosis of NLD-SFN.

Methods:
We performed a retrospective review of 1000 consecutive patients referred for skin biopsy. Skin biopsies were taken from the posterior cervical, distal thigh and distal leg regions and were immunostained with PGP9.5. Analysis of IENFD was completed using standard counting rules with immunofluorescent imaging. Biopsies from the posterior cervical region have IENFD>30 fibers/mm, distal thigh 8-19 fibers/mm, and distal leg 3-12 fibers/mm. We determined that IENFD >30 fibers/mm at the distal leg or distal thigh were mislabeled.

Results:
Of 1000 consecutive cases, 421 had reduced IENFD at one or more biopsies (354 length-dependent and 67 with a non-length dependent distribution). Of the 67 cases with NLD-SFN, 57 had distal IENFD>30 fibers/mm indicating mislabeling of the posterior cervical specimen. The remaining 9 NLD-SFN cases had either severe reduction at all biopsy sites (N=4) or had selective reduction in one or more proximal biopsy sites with normal distal biopsies (N=5).

Conclusions:
We identified 421 individuals with reduced IENFD of which 67 were non-length dependent. Of these, 87% had IENFD higher than the upper limits of normal for distal leg and thigh sites, consistent with posterior cervical IENFD counts. These findings suggest that specimen mislabeling occurs in approximately 5% of cases. We recommend caution in interpreting abnormal biopsy results that are inconsistent with the history and examination findings, particularly when the proximal to distal nerve fiber density gradient appears to be reversed.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: small fiber, Non length dependent, Neuropathy, Skin biopsy

Multifactorial Brachial Neuralgia.

Poster No:
P 210

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Introduction:
Objectives: to identify the osteoarticular risk factors responsible for brachial neuralgia resistant to conventional therapy.

Methods:
Case study followed up in the framework of the specialized consultation of occupational pathologies.

Results:
A doctor aged about fifty. The pain was stabbing at the level of the left shoulder stump, and accompanied by shifting pain points at the level of the forearm, the cervices' and dorsal stage. The follow-up in functional rehabilitation mentions a tendinitis with prescription of analgesics and corticoids. We recommended Joint mobilization of the left shoulder without a sling and hot baths. The pain became throbbing, disabling, exacerbated by coughing, distressing and resistant to therapy. A second doctor recommended two sessions of infiltration with acupuncture. The biological assessment showed an inflammatory syndrome. Ultrasound showed a liquid layer in the synovial sheath of the long head of the biceps. MRI of the shoulder concluded that there was non-calcifying insertion tendinopathy of the supraspinatus and infraspinatus tendons with a subchondral bone cyst of the major tubercle at the level of their enthesis. The biological assessment showed hyperglycemia and glycated hemoglobin at 12.2%. The brachial neuralgia caused by a brutal sports activity and aggravated by the professional activity (repetitive movements with a fast cadence and an important workload (the subject is an author). Besides the hostile work environment and stress (requisitioning for on-call duty in Covid-19 units, problems of harassment at work,...).

Conclusions:
rotator cuff tendonitis is multifactorial and deserves a multidisciplinary approach (ergonomic and psychosocial analysis, etc.).

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Yes

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Grant Support:

Keywords: Rotator cuff, Metabolic tendinopathy, Occupational tendinopathy, Pain, Professional stress

Non-invasive evaluation of peripheral nerve stiffness in people with distal symmetric polyneuropathy as potential biomarker of disease progression

Poster No:
P 211

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Introduction:
Shear wave velocity, as measured by using ultrasound shear wave elastography, is a promising indicator of peripheral nerve mechanical properties, such as stiffness. How these mechanical properties may alter in people with diabetes with and without distal symmetrical polyneuropathy (DSPN) is largely unknown with the disease progression.

Methods:
This cross-sectional study aimed to quantify and compare peripheral nerve shear wave velocity of sural, tibial, and median nerves between healthy participants (n=27), people with diabetes without DSPN (n=10), people with DSPN in the lower limbs only (DSPN FEET; n=19), and people with DSPN in the upper and lower limbs (DSPN HANDS & FEET; n=21). DSPN was confirmed with electrodiagnosis and corneal confocal microscopy. Linear mixed-models were used to detect differences in sural, tibial, and median shear wave velocities across groups. Receiver operating characteristic (ROC) curve analysis and area under the curve (AUC) were calculated to determine diagnostic performance between DSPN and no DSPN groups.

Results:
Sural and tibial shear wave velocities were increased in DSPN HANDS & FEET and DSPN FEET, but only tibial shear wave velocity increased in DSPN HANDS & FEET. No changes were observed for the median nerve across groups. The diagnosis utility of shear wave velocity to detect DSPN was good for the sural nerve (AUC: 0.76). The optimal cut-off values was a sural shear wave velocity of 7.93 m/s.

Conclusions:
Shear wave elastography is a useful tool to assess the progression and severity of DSPN.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Diabetic Neuropathy, Tissue Elasticity Imaging , Peripheral Nerves , Diagnostic Imaging , Ultrasonography

Activation of Keratinocyte Gq-linked GPCRs Enhances Dorsal Root Ganglion Neuron Voltage-Gated Sodium Channel Activity and Neuronal Excitability

Poster No:
P 212

Authors:
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Institutions:
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Introduction:
Epidermal Keratinocytes (K14) are closely juxtaposed to cutaneous nerve terminals, enabling bidirectional communication. To investigate potential mechanisms that mediate this communication, we genetically expressed stimulatory DREADDs (hM3Dq) into K14 cells as a tool for mimicking the activation of Gq-linked GPCRs in K14 cells in mice. We observed that CNO activation of hM3Dq induced an increase in depolarization induced [Ca2+]i responses in their DRG neurons. We hypothesized that the increased [Ca2+]i responses reflected changes in voltage-gated ion channel function, including sodium channels.

Methods:
Whole-cell patch-clamp experiments were performed in DRG neurons acutely isolated from both CNO and control mice. All recordings, voltage-clamping and data acquisition were made using SynchroPatch 384 (Nanion, Germany).

Results:
Analysis of the biophysical properties of Nav channels showed that there is an increase in the current amplitude in CNO compared to control mice. We next measured the normalized conductance and found that there is a significant shift in the depolarized direction of the midpoint voltage. We also observed larger peak currents as evidenced by measuring the time to peak. Furthermore, we found an increased percentage of DRG neurons in the CNO groups that displayed Nav currents compared to control. Preliminary analysis of APs indicated that there was an increase in evoked AP generation in CNO compared to control mice.

Conclusions:
These data indicate that activation of basal keratinocytes Gq-linked GPCRs resulted in alterations in the biophysical properties of sodium channels in accompanying DRG neurons: in particular, we noted an increase in sodium current amplitude. Changes in Nav function have been shown to be associated with excitability disorders including neuropathic pain (1-3). Our results indicate that keratinocytes can regulate the excitability of DRG neurons and suggest possible therapeutic effects of activating or blocking specific keratinocyte Gq-linked GPCRs as a mechanism for modulating neuronal excitability in chronic disorders of pain and itch.

References:
Yes

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References 2:
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Chen L, Huang J, Zhao P, et al. Conditional knockout of Na(V)1.6 in adult mice ameliorates neuropathic pain. Sci Rep. 2018;8(1):3845.

Grant Support:

Keywords: keratinocytes, DRG neurons, excitability, GPCR, Voltage-gated sodium channels

Worsening Diabetic Neuropathy And Foot Drop In Poorly Controlled Diabetes Mellitus But Low HBA1C.

Poster No:
P 213

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Institutions:
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Introduction:
Diabetic peripheral neuropathy is one of the most common complications of Diabetes Mellitus and it may affect over 50% of patients. It is related to chronic hyperglycaemia. It classically demonstrates a sensory predominant glove and stocking pattern of deficits. The nerves are also prone to compression injury at common entrapment sites.

Methods:
A 42 year old female presented with a 3-month history of progressive difficulty walking, tingling sensation and numbness in both her lower limbs . She has no low back pain, blurred vision or upper limb weakness. She is a known Diabetic, non-compliant on her insulin therapy; has had two admissions for hyperglycemia. She also had for an acute kidney injury from urosepsis 5 months ago. She had been anaemic since teenage years. She had no history of menorrhagia, normal iron, autoimmune and electrophoresis studies. In addition she had a severe left foot drop with clinical signs localising the pathology (likely compression) to the fibula neck.

Results:
Patient's haemoglobin was 8g/dl and HBA1C 6.6% The low HBA1C is likely related to her anaemia. Alternatively it could also indicate precipitous improvement in her glycaemic control. Such sudden and massive improvement in diabetic control can acutely worsen background diabetic polyneuropathy ; and in turn predispose to compression neuropathies. This phenomenon is known as treatment induced neuropathy of diabetes mellitus, (TIND). The rest of the evaluation including, ANA/anti-dsDNA, thyroid function, B12, folate levels, HIV were unremarkable.

Conclusions:
Peripheral neuropathy is a common complication for poorly controlled diabetes mellitus. In addition, patients with diabetic neuropathy are prone to compression neuropathy at common entrapment sites. Symptomatic worsening of the neuropathy symptoms, as well as entrapment mononeuropathies, may be more common in the context of sudden and rapid improvement in glycaemic control.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: diabetes mellitus, peripheral neuropathy, foot drop, compression neuropathy

Adaptive autonomic and neuroplastic control in diabetic neuropathy: a narrative review

Poster No:
P 214

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Introduction:
Type 2 diabetes mellitus (T2DM) is a worldwide burden to many individuals, as well as to socio-economic and healthcare systems. T2DM is generally accompanied by a variety of metabolic and hemodynamic disorders, as well as nerve dysfunction referred to as diabetic neuropathy (DN). Despite a tremendous body of research, the pathogenesis of DN remains largely elusive. Currently, two schools of thought exist regarding the pathogenesis of diabetic neuropathy: a) mitochondrial-induced toxicity and neuronal programmed death, and b) microvascular damage and consequent neural degeneration. Both mechanisms signify diabetic neuropathy as an intractable and irreversible disease and, as a consequence, therapeutic approaches focus on treating symptoms with limited efficacy and an elevated risk of side effects.

Methods:
This paper, in contrast to current approaches, proposes that the human body exclusively employs mechanisms of adaptation to protect itself during an adverse event. For this purpose, two control systems are defined, namely the autonomic - and the neural control systems, both playing a role in generating distinct adaptive cascades to maintain homeostasis. The autonomic control system responds via inflammatory and immune responses, while the neural control system regulates neural signaling, via plastic adaptation, at both peripheral and central levels. Both systems are proposed to regulate a network of temporal and causative connections which unravel the complex nature of diabetic complications. For example, peripheral neuroplastic events may play a major adaptive role in diabetic neuropathy using restorative mechanisms, similar to what has been explored in brain development and phantom limb syndromes.

Results:
A significant result of this approach infers that both autonomic and neuroplastic adaptations make diabetic neuropathies, and other diabetic-related complications, reversible.

Conclusions:
In conclusion, the proposed model may open the door to novel therapeutical applications which could trigger the restorative abilities of both the autonomic and neural control.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: N/A

Keywords: Diabetes, Diabetic Neuropathy, Adaptive Control Systems, Autonomic Control System, Neural Control System

Diabetes Combined with COVID-19 (SARS-CoV-2) Infection Increases the Relative Risk of Developing Neuropathy

Poster No:
P 215

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Institutions:
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Introduction:
Patients with diabetes mellitus (DM) are more likely to have severe complications with COVID-19 (SARS-CoV-2). However, the impact of COVID-19 on increasing risk of diabetic neuropathy, is unknown.

Methods:
To determine the relative risk of developing diabetic neuropathy, we used the TriNetX database, a global federated health research network providing access to electronic medical records from a network of 79 global health care organizations. Subjects were entered prospectively from January 2020 to December 2022 and were coded for neuropathy, type 2 diabetes mellitus (DM2), or COVID-19 by ICD10 code. The two tested groups were 1) DM2 + neuropathy (D+N) and 2) DM2 + COVID-10 + neuropathy (D+C+N). Propensity matching, from more than 2.5 million subjects, was performed between the two groups using 32 covariates. Each matched group had more than 200,000 subjects. The relative risk of newly diagnosed neuropathy (after January 2020) in subjects with DM2 +/- diagnosed COVID-19 was tested to determine a risk ratio (RR) based on the relative risk for each group.

Results:
After 1 month, the risk ratio (RR) between the 2 groups (D+C+N vs. D+N) was 1.277 (CI 1.21;1.348, $p<0.0001$, OR 1.281, CI 1.213;1.353) but increased to a maximum RR of 1.382 at 3 months (risk 2.06 vs 1.49, RR 1.382 $p <0. 0001$, CI 1.32;1.448, OR 1.391, CI 1.326;1.458). The RR continued to gradually fall in subjects retained in the cohort for 2 years (RR 1.069, $p<0.0001$, OR 1.071).

Conclusions:
In a large international database, DM2 alone increased risk of developing neuropathy. However, infection with COVID-19, in propensity matched cohorts, significantly further increased the risk of developing neuropathy. The greatest RR occurs within 3 months of infection. The RR then gradually declined over 2 years, indicating that the RR of developing neuropathy, in subjects with DM2, decreases with time since COVID-19 infection.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Diabetes, COVID-19, Neuropathy

Clinical Neuropathy Measures Of Natural History Progression In Neuropathy Associated With Metabolic Syndrome

Poster No:
P 216

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Institutions:
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Introduction:
Natural history progression of neuropathy is critical to appropriately power clinical trials. However, expected natural history change in phenotypic measures for peripheral neuropathy associated with metabolic syndrome (NiMS) have not been well delineated.

Methods:
Participants, with early NiMS, evaluated in previous cross sectional studies, or participating as controls in previous randomized trials of behavioral interventions, were invited to return for repeat evaluation of a key set of phenotyping measures. Obtained measures include the Norfolk Quality of Life for Diabetic Neuropathy (NQoLDN), the Utah Early Neuropathy (exam) Scale (UENS), 3 mm punch biopsy for intraepidermal nerve fiber density (IENFD), and select nerve conduction studies.

Results:
To date, 16 patients (6 female) have met inclusion criteria. Average age at follow-up was (mean +/- SD) 70.19 +/- 7.31 years. At follow-up, 14/16 were characterized as having type 2 diabetes, 1 as having type 1 diabetes and one metabolic syndrome. The average follow-up period was 6.72 +/- 0.80 years. NQOL-DN worsened 14.53 +/- 14.07, 2.21 points per year. Baseline UENS was 7.44 +/- 5.76. 11/16 had a baseline UENS score greater than 4, consistent with neuropathy, and 15/16 had a UENS score greater than 4 at follow-up. Over the follow-up period, UENS score increased by 3.63 +/- 5.47, an average progression of 0.54 points per year. 2 of 16 participants demonstrated an improvement in UENS score over the follow-up period, but no participants showed entire loss of their symptoms. IENFD at distal leg (n=6) declined 1.62 +/- 2.82 fibers/mm, -0.23 +/- 0.404 per year. Distal thigh IENFD (n=4) declined only 0.01 +/- 0.48 per year.

Conclusions:
In this NiMS cohort, clinical measures (UENS, NQOL-DN) showed greater dynamic range than structural progression measures, like nerve conduction studies and IENFD. This supports use of clinical measures as endpoints in future clinical trials.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Neuropathy, Metabolic Syndrome, Biomarkers

Neuropathic pain in diabetic polyneuropathy

Poster No:
P 217

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Introduction:
Diabetic polyneuropathy (DPN) is a common complication of type 2 diabetes (T2D). Up to 50 % of patients with DPN suffer from neuropathic pain (P-DPN). The relationship between severity in sensory symptoms, signs and the development of pain in DPN is relatively unstudied. Neuroinflammation is thought to contribute to the development of DPN and P-DPN. There is a lack of prospective studies on DPN and P-DPN.

Methods:
Originally, 389 patients with newly diagnosed T2D and a likelihood of polyneuropathy as assessed by questionnaire and 97 healthy controls were recruited to establish the diagnosis of DPN. All participants from the baseline study will be invited for a 5 year follow up examination

Results:
As of November 1st 2022 303 participants have been invited and 149 participants (follow-up rate: 49 %) have agreed to a follow-up visit. Of these, 119 participants (91 diabetes patients + 28 controls) have completed the examinations. Mean follow-up time was 4.6 (SD 0.7) years and mean diabetes duration was 6.1 (SD 2.6) years and 10.8 (SE 2.6) years at baseline and follow-up, respectively. 20.9 % had painful DPN at baseline, which decreased slightly to 19.8 % at follow-up. 7.7 % had developed neuropathic pain while 8.8 had experienced remission of pain. Data on symptoms and diagnostic changes are currently being processed and the study is ongoing

Conclusions:
With the lack of prospective studies in DPN, this study will provide a unique insight into the natural history of DPN and P-DPN.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: IDNC Steno Diabetes Center, AUH Novo Nordisk Foundation

Keywords: Diabetes, Neuropathic Pain, Neuropathy, Clinical research, Sensory symptoms

Lumbosacral Radiculoplexus Neuropathy (LRPN) is not a benign condition.

Poster No:
P 218

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Introduction:
Diabetic and idiopathic lumbosacral radiculoplexus neuropathy (LRPN) is a disabling condition with subacute onset of severe pain and asymmetric weakness in lower extremities. Progression typically occurs over weeks to months followed by partial to full recovery. Although small retrospective studies have shown beneficial effects of immunomodulatory therapy, no published controlled trials are available.

Methods:
We present our experience of diabetic and idiopathic LRPN in a tertiary care practice. Retrospectively analysis was done for all patients with this diagnosis for the last four years. One of the two neuromuscular physicians evaluated all patients including performing electrodiagnostic studies.

Results:
25 patients (Median age 67; 14M, 11 W), 19 with diabetes (median HbA1c 8.05) were included. All presented with subacute onset of weakness in the lower extremities. 22 patients had significant pain. 11 noted weight loss exceeding >10 lbs. Proximal weakness (hip flexion and knee extension) was prominent in 12; distal weakness (dorsiflexion) weakness was prominent in six; and proximal and distal weakness in 7. Mean lower limb MRC sum score was 22.8. In 9, the presentation was unilateral. In all patients, electrodiagnostic studies showed axonal loss in the distribution of lumbar plexus (18); femoral nerve (23); obturator nerve (18); lumbosacral plexus (8); common fibular neve (18) and tibial nerve (6). Localization was confirmed to be distal to the dorsal root ganglia in 23. 3 patients were treated with IV steroids. All patients stabilized but improvement was only mild and occurred in 14 patients (mean follow-up 13 months).

Conclusions:
Diabetic and non-diabetic LRPN is a severe condition with continual morbidity and disability. In majority of the patients, the localization is at the plexus or nerve level, suggesting that LPN rather than LRPN is a more appropriate nomenclature. Distal, especially dorsiflexion, weakness is frequent. Controlled studies are needed in attempts to alter the significant disability associated with this condition.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Diabetes, amyotrophy, radiculoplexusneuropathy, lumbar plexopathy

Degeneration of RAGE and Cutaneous Blood Vessels at the Distal Limb of Diabetic Sensory Neuropathy Subjects

Poster No:
P 219

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Institutions:
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Introduction:
We assessed dermal neurovascular innervation in diabetic patients presented with diabetic sensory polyneuropathy (DSPN). intraepidermal nerve fibers (IENF), dermal Schwann cells (SC), capillaries (BV), and expression of Receptors for Advanced Glycation End products (RAGE) were assessed in distal leg skin punches. RAGE is a transmembrane receptor that binds altered glycoproteins and initiates a proinflammatory reaction. RAGE activation has been linked to degenerative diseases while inhibition has had protective effects.

Methods:
20 patients and 20 age/gender-matched healthy subjects were included. All subjects underwent neurological examinations, 3mm skin punches at the distal leg (DL), and proximal thigh (PT). 50µm sections were immunohistochemically stained for PGP9.5 (IENFD; fibers/mm) anti-p75 (SCD; cells/mm3), anti- CD 31 (BVD; mm/mm3) and anti-RAGE (fibers/mm2). Immunofluorescence sections were assessed under LSM510 confocal imaging system to localize co-expression of RAGE on axons and vessels. Measurements were performed using established unbiased stereological techniques.

Results:
IENFD ($p<0.0001$ and BVD ($p<0.001$) were significantly reduced across the lower limb in DSPN subjects vs. healthy controls and SC ($p<0.01$) at the DL. RAGE was robustly expressed both on dermal myelinated and unmyelinated axons and along the basement membrane of arterioles/venules at the upper dermis. In DSPN subjects the blood vessels exhibited absence of intra papillary hairpin loops and ended as blunt stumps with the overlying epidermis exhibiting vacuolation. Blood vessel density pattern at the lower limb significantly correlated with IENFD ($r=0.37$, $p<0.001$) and RAGE+ve fibers ($r=0.54$, $p<0.001$) and with Schwann cells at the DL ($r=0.46$, $p=0.004$).

Conclusions:
We conclude that in DSPN, RAGE+ve structures are susceptible to damage. Epidermal nerve fiber loss is correlated with blood vessel damage across the limb and is consistent with a vascular etiology for DSPN.

References:
Yes

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References 4:
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Grant Support:

Keywords: RAGE, Blood vessels, Epidermal nerve, Diabetes, Neuropathy

Ketolysis is Required for Proper Development and Function of the Somatosensory Nervous System.

Poster No:
P 220

Authors:
Jonathan Enders[1], Jarrid Jack[2], Sarah Thomas[2], Paige Lynch[2], Sarah Lasnier[2], Xin Cao[2], M Swanson[2], Janelle Ryals[2], John Thyfault[2], Patrycja Puchalska[3], Peter Crawford[3], Douglas Wright[2]

Institutions:
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Introduction:
Ketogenic diets are emerging as protective interventions in preclinical and clinical models of somatosensory nervous system disorders. Additionally, dysregulation of SCOT (encoded by Oxct1), the fate-committing enzyme in mitochondrial ketolysis, has recently been described in Friedreich's ataxia and amyotrophic lateral sclerosis. However, the contribution of ketone metabolism in the normal development and function of the somatosensory nervous system remains poorly characterized.

Methods:
We generated sensory neuron-specific, Advillin-Cre knockout of Oxct1 (SNACKO) mice and characterized the structure and function of their somatosensory nervous system. We used histological techniques to assess sensory neuronal populations, myelination, and skin and spinal dorsal horn innervation. We examined cutaneous and proprioceptive sensory behaviors with the von Frey test, radiant heat assay, rotarod, and grid walk tests.

Results:
SNACKO mice exhibited myelination deficits, altered morphology of putative Aδ soma from the dorsal root ganglion, and reduced epidermal innervation compared to wildtype mice. SNACKO mice also exhibited abnormal innervation of afferent fibers within the spinal dorsal horn. Loss of peripheral neuronal ketolysis was further associated with proprioceptive deficits, yet SNACKO mice did not exhibit drastically altered cutaneous mechanical and thermal thresholds.

Conclusions:
We report that the knockout of Oxct1 in peripheral sensory neurons resulted in histological abnormalities and severe proprioceptive deficits in mice. We conclude that ketone metabolism is essential to normal sensory functions of the PNS. These findings also suggest that loss of ketone metabolism in the peripheral sensory nervous system may explain the neurological symptoms experienced in Friedreich's ataxia.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: This work was supported by NIH grants R01 NS043314 (DEW), R01 AG069781 (PAC and JPT), R01 DK091538 (PAC), the Kansas Institutional Development Award (IDeA) P20 GM103418, Kansas University Training Program in Neurological and Rehabilitation Sciences NIH T3

Keywords: Ketolysis, Friedreich's Ataxia, Dysmyelination, Neuropathy, Somatosensation

ATP-Gated Potassium Channels Contribute to Ketogenic Diet-Mediated Analgesia.

Poster No:
P 221

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Introduction:
Chronic pain is a substantial health burden, affecting 18-20% of American adults. Options for treating chronic pain remain minimally effective. Ketogenic diets are emerging as effective therapeutic strategies in preclinical models of chronic pain, especially diabetic neuropathy. Here, we tested the hypothesis that a ketogenic diet provides analgesia through ketone oxidation and subsequent activation of ATP-gated potassium (KATP) channels.

Methods:
We fed mice a ketogenic diet one week before intraplantar injection of noxious stimuli (methylglyoxal, cinnamaldehyde, or capsaicin) and determined mechanical withdrawal threshold by Von Frey testing or observed nocifensive responses (licking, biting, lifting, etc.) five minutes after injection. We quantified p-ERK+ cells in the spinal dorsal horn 10 minutes after noxious injection as a surrogate of spinal activation. We used sensory-neuron-specific Advillin-Cre knockout of Oxct1 (SNACKO) mice to determine the contribution of ketone oxidation. We delivered tolbutamide (antagonist, 8 μg) or diazoxide (agonist, 115 ng) before noxious stimulus to inhibit or activate KATP channels, respectively.

Results:
Methylglyoxal, cinnamaldehyde, and capsaicin evoked nocifensive behaviors and upregulated spinal activation markers (p-ERK+) in chow-fed mice following intraplantar injection. Mice fed a ketogenic diet were protected from noxious stimulus-evoked nociception and elevations in spinal dorsal horn activation. Consuming a ketogenic diet incompletely prevented methylglyoxal-evoked nociception in SNACKO mice, indicating ketone oxidation is required for full analgesia-like effects provided by a ketogenic diet. Tolbutamide injection in ketogenic diet-fed mice blocked the anti-nociceptive effect of the diet and restored spinal dorsal horn activation. In chow-fed mice, diazoxide recapitulated the ketogenic diet-induced analgesia to capsaicin and block of spinal activation.

Conclusions:
These data support a cellular mechanism by which a ketogenic diet leds to changes in ketone oxidation and activation of KATP channels to provide analgesia. Further, these findings identify KATP channels as druggable targets to recapitulate the analgesic effect of a ketogenic diet.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: This work was supported by NIH grants R01 NS043314 (DEW), R01 AG069781 (PAC), R01 DK091538 (PAC), the Kansas Institutional Development Award (IDeA) P20 GM103418, Kansas University Training Program in Neurological and Rehabilitation Sciences NIH T32HD05785

Keywords: Ketogenic Diet, K-ATP Channels, Pain, Methylglyoxal, Sulfonylureas

Adipo-glial signaling mediates metabolic adaptation in peripheral nerve regeneration

Poster No:
P 222

Authors:
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Institutions:
[1]Institute of Anatomy, Leipzig, Germany, [2]Paul Flechsig Institute of Neuropathology, Leipzig, Germany

Introduction:
The peripheral nervous system harbours a remarkable potential to regenerate after acute nerve trauma. Full functional recovery, however, is rare and critically depends on peripheral nerve Schwann cells that orchestrate break down and resynthesis of myelin and, at the same time, support axonal regrowth. How Schwann cells meet the high metabolic demand required for nerve repair remains poorly understood.

Methods:
We employ experimental nerve crush in a series of conditional mouse mutants to assess the metabolic response of Schwann cells to nerve injury. We abolish either leptin receptor function from Schwann cells, or leptin expression in adult adipocytes, to study adipo-glial communication in nerve regeneration.

Results:
We here report that nerve injury induces adipocyte to glial signaling, and identify the adipokine leptin as an upstream regulator of glial metabolic adaptation in regeneration. Signal integration by leptin receptors in Schwann cells ensures efficient peripheral nerve repair by adjusting injury-specific catabolic processes in regenerating nerves, including myelin autophagy and mitochondrial respiration.

Conclusions:
Our findings propose a model according to which acute nerve injury triggers a therapeutically targetable intercellular crosstalk that modulates glial metabolism, to provide sufficient energy for succesful nerve repair.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: DFG Emmy Noether (FL1025-1-1)

Keywords: Schwann cell, acute nerve injury, nerve regeneration, adipocyte, metabolism

Opening of Kv7 Channels Activates AMPK and Mimics Aspects of Antimuscarinic Drug Action in Adult Sensory Neurons

Poster No:
P 223

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Introduction:
Voltage-gated potassium channels (Kv7) are regulators of cellular physiology and controlled, in part, by G protein-coupled receptors. The most abundant subunits of Kv7 in sensory neurons are Kv7.2/7.3 (M-channels). Currents passing through M-channels are low-threshold, slowly activating potassium currents that maintain a negative resting membrane potential to prevent hyperexcitability. Development of selective modulators for Kv7 channels represent a novel and exciting therapeutic target in the treatment of neurodegenerative diseases, including neuropathic pain. Antagonism of muscarinic acetylcholine type 1 receptor (M1R) using pirenzepine (PZ) induced AMP-activated protein kinase (AMPK) activity and augmented mitochondrial function to enhance nerve repair in neuropathic disease. This project aimed to determine mechanisms of action of antimuscarinic drugs, at the M1R, with a focus on modulation of Kv7. We hypothesized that M1R antagonism via activation of Kv7.2/7.3 enhanced mitochondrial function to modulate sensory neuron excitability and provide neuroprotective effects.

Methods:
Dorsal root ganglia (DRG) sensory neuron cultures from adult control or streptozotocin (STZ)-induced diabetic rats were treated with PZ (1μM) or Kv7 opener retigabine (10μM). Cellular bioenergetic status was assessed using a Seahorse XF-24. Cultured DRG neurons were loaded with voltage sensor probe DiBAC4(3) to evaluate the plasma membrane potential. Expression analysis of AMPK was performed by Western blot and neurite outgrowth assessed using immunocytochemistry.

Results:
PZ or retigabine treatment significantly increased AMPK phosphorylation and ATP production in cultures derived from control or diabetic rats. Both drugs similarly induced hyperpolarization. The effect of retigabine was blocked by the selective Kv7 blocker, XE991 (15μM). DRG cultures from diabetic rats exhibited a significant 2-3-fold elevation in neurite outgrowth in response to PZ or retigabine (with no additive effect when combined).

Conclusions:
These findings reveal that antagonism of M1R activates Kv7.2/7.3 to elevate mitochondrial function and support axonal regeneration in neurodegenerative disease. Funding: MITACs # IT14860 and WinSanTor Inc.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: MITACs # IT14860 and WinSanTor Inc.

Keywords: Axon, Diabetic neuropathy, Dorsal root ganglia, Mitochondria, Plasma membrane potential

Choline Acetyltransferase Regulates The Neuritogenic Phenotype Of Adult Sensory Neurons

Poster No:
P 224

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Introduction:
Choline acetyltransferase (ChAT) is the key enzyme that catalyzes the biosynthesis of the neurotransmitter acetylcholine, an agonist of the muscarinic acetylcholine type 1 receptor (M1R). We have recently made the discovery that suppression of M1R signaling elevates neurite outgrowth in adult sensory neurons. However, the regulatory role of ChAT in sensory neuritogenic phenotype remains elusive.

Methods:
Western blot, immunostaining and gene knockdown studies were performed in cultured dorsal root ganglion (DRG) neurons and/or intact DRG tissues collected from adult male Sprague–Dawley rats, C57BL/6 mice or M1R knockout mice on a C57BL/6 background.

Results:
Here we report that the ChAT protein expression was significantly upregulated in response to NGF and NT-3 and downregulated by GDNF treatment in dissociated adult rat DRG neurons. Immunostaining studies confirm the cholinergic phenotype of DRG neurons with ChAT, AChE and VAChT expression. We utilized a fluorescent dye ATTO590-labeled muscarinic toxin 7, a specific negative allosteric modulator of M1R, to confirm the presence of M1R in all subpopulations of DRG neurons. In DRG culture, knocking down ChAT mRNA using neuron-specific adeno-associated virus AAVPHP.S, which delivered ChAT-shRNA, significantly increased neurite outgrowth compared to scrambled-shRNA. In contrast, AAVPHP.S-delivered ChAT-shRNA exerts no additional effect on neurite outgrowth in neurons lacking M1R when compared with wild-type controls.

Conclusions:
Taken together, our findings demonstrated that the modulation of ChAT expression is sufficient to regulate neuritogenic phenotype in adult sensory neurons. This data clarifies the mechanisms of cholinergic constraint on neurite outgrowth and will enable the development of novel therapeutics for peripheral neuropathy. CIHR# PJT-162172.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: Funding: CIHR# PJT-162172.

Keywords: Axon, Diabetic neuropathy, Dorsal root ganglia, Choline acetyltransferase , Neurite outgrowth

Early Ultrastructural Lesions of ANCA- vs Complement-Associated Vasculitis

Poster No:
P 225

Authors:
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Institutions:
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Introduction:
This study aims to describe electron microscopic findings of vasculitis associated with anti-neutrophil cytoplasmic antibody (ANCA) and complement.

Methods:
Sural nerve biopsy specimens were obtained from ten patients with microscopic polyangiitis (MPA), a representative ANCA-associated vasculitis, and six patients with nonsystemic vasculitic neuropathy (NSVN), who were negative for ANCA but positive for complement deposition. For electron microscopy, epoxy-resin-embedded specimens were cut into 70-nm-thick ultrathin transverse sections using an ultramicrotome. Sections were placed on a square 100-mesh copper grid of 250-μm pitch and 200-μm hole, stained with uranyl acetate and lead citrate, and viewed under a transmission electron microscopy.

Results:
In patients with MPA, the attachment of neutrophils to epineurial vascular endothelial cells, the migration of neutrophils to the extravascular space via the penetration of the endothelial layer, and the release of neutrophil components to the extracellular space were observed. Such neutrophil-associated lesions were not observed in patients with NSVN. Nonetheless, morphological changes in epineurial vascular endothelial cells, such as increases in cytoplasmic organelles and cytoplasmic protrusions into the vascular lumen, were observed in patients with NSVN. Since these findings were observed where light microscopy-based findings suggestive of vasculitis (e.g., the disruption of vascular structures and fibrinoid necrosis) were absent, they were considered early lesions that preceded the formation of the so-called necrotizing vasculitis.

Conclusions:
This study enabled the visualization of distinctive early ultrastructural lesions associated with ANCA and complement. Further studies are needed to elucidate the molecular basis of the induction of these fine structural changes, which will contribute to the development of targeted therapies based on specific mechanisms of vasculitis.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: vasculitis

Large fiber dysfunction progress in parallel with small fiber dysfunction in diabetes mellitus. A study with sudoscan and nerve conduction study

Poster No:
P 226

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Institutions:
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Introduction:
It has been reported that Sudoscan (SS) works well in detecting diabetic small fiber neuropathy, however, it is not clear if the electrochemical conductance (ESC) of SS decline earlier than the large fiber dysfunction in diabetic polyneuropathy (DPN). We then evaluated ESC values and results of nerve conduction studies (NCS) in the lower limb of patients with Type2 diabetes mellitus (T2DM).

Methods:
We carried out SS and NCS in 168 patients with T2DM. Since DPN is a length-dependent axonal neuropathy, ESC of the feet was evaluated and sural SNAP and foot muscle CMAP evoked by supramaximal tibial nerve stimulation were recorded. We estimated the severity of the large fiber dysfunction after Baba's DPN severity criteria (BDC) by NCS as follows; BDC-0: No NCS abnormalities, BDC-1: Delay in any of SNAP, CMAP and/or F-wave, BDC-2: Fall in SNAP amplitude below 5μV, BDC-3: Fall in CMAP amplitude between 2 and 5mV, BDC-4: Fall in CMAP amplitude below 2mV.

Results:
ESC in the subjects with neither neuropathic signs nor NCS abnormalities was 78.1±5.0μS, from which we set 70μS as cut-off value of the feet ESC. Forty-seven percent of the subjects showed low ESC less than 70μS, while NCS was abnormal in 79% of the subjects: F-wave latency was the most frequent abnormality. BDC-0 group had ESC of 73.5±12.6μS, while all patients with BDC-3&4 had abnormally low ESC of 10-62μS. Statistically significant correlation ($p<0.001$) was confirmed between progression in BDC and fall in ESC. On the other hand, 5% of BDC-0 subjects showed ESC less than 70μS (lowest:16μS).

Conclusions:
Although small fibers may be involved earlier than large fiber, large fiber dysfunction revealed by NCS progress almost parallel to small fiber dysfunction in T2DM.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: diabetic neuropathy, sudoscan, nerve conduction study, small fiber , large fiber

The Effect of Global Nox4 Deletion on Prediabetic Peripheral Neuropathy

Poster No:
P 227

Authors:
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Introduction:
Prediabetes affects approximately 541 million individuals worldwide, of which 30% suffer from peripheral neuropathy (PN). Dyslipidemia is an important mediator of pre-diabetic PN. However, the mechanisms by which dyslipidemia leads to injury are unknown. While dyslipidemia favors a highly oxidizing environment, how dyslipidemia intersects with specific sources of reactive oxygen species (ROS) to produce nerve damage is unclear. NADPH oxidase (Nox) enzymes are dedicated for ROS production, and of the 7 members (Nox1-5, Duox1 and 2), the Nox4 isoform is implicated in nerve degeneration and diabetic PN. Here, our aim was to evaluate whether Nox4 global deletion could improve metabolic parameters and nerve function in the high-fat diet (HFD)-fed mouse model of PN

Methods:
HFD-associated changes in PN were assessed in 12-week-old C57BL/6J male WT and Nox4 knockout (KO) mice. Body weights and pain behaviors were measured monthly. After 24 weeks of HFD, metabolic and PN phenotyping as well as western blotting were performed.

Results:
Although KO mice gained weight at a slower pace compared to WT mice, both HFD and KO-HFD mice were significantly heavier than their respective controls at study termination. Both HFD and KO-HFD mice also had impaired glucose tolerance. While Nox4 deletion ameliorated thermal sensitivity after 12 weeks of HFD, this effect was abolished at study termination. Additionally, Nox4 deletion had no effect on large fiber function at early and later disease stages. We next determined whether Nox4 deletion triggered a compensatory induction of other Nox isoforms and found a significant increase in Nox2 protein expression in KO mice with or without HFD relative to WT mice on a standard diet

Conclusions:
These results suggest that increased Nox2 expression may mediate HFD-induced nerve dysfunction in the absence of Nox4. Thus, therapies aimed at normalizing Nox levels rather than completely silencing them may be promising therapeutic approaches for PN treatment.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: Funding information: Financial support for this work provided by the NIDDK Diabetic Complications Consortium (RRID:SCR_001415, [www.diacomp.org]www.diacomp.org), grants DK076169 and DK115255.

Keywords: Preddiabetes, peripheral neuropahty, reactive oxygen species, high fat diet

Effects of progressive resistance training on muscle volume, fat infiltration, muscle strength in individuals with and without diabetic polyneuropathy

Poster No:
P 228

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Institutions:
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Introduction:
To evaluate the effects of progressive resistance training (PRT) on muscle strength, total muscle volume (TMV) and fat infiltration of skeletal muscles in individuals with type 2 diabetes with and without diabetic polyneuropathy (DPN) compared to healthy controls (HC).

Methods:
In this assessor blinded trial we included individuals with type 2 diabetes with DPN (n=27), without DPN (n=24) and HC (n=29). All three groups were randomized to either PRT or non-PRT (1:1) for 12 weeks. At baseline and following 12 weeks, individuals underwent magnetic resonance imaging of the non-dominant lower extremities and maximal isokinetic muscle strength was determined.

Results:
PRT resulted in muscle strength gains of the knee extensors and flexors in all groups using comparative analyses [DPN: non-PRT: 0.6 (-7.1; 2.8) vs. PRT: 8.7 (3.6; 19.9); non-DPN: non-PRT: 4.8 (-0.6; 6.7) vs. PRT: 9.3 (3.6; 13.6); HC: non-PRT: 0.0 (-8.9; 1.5) vs. PRT: 5.7 (-0.5; 13.3) $p<0.05$ for all]. Following PRT, individuals with diabetes without DPN improved TMV of the knee flexors [non-PRT-81.3 (-249.7; 87.1) vs. PRT: 161.6 (108.5; 214.7) p=0.03] and fat fractions (FF) [non-PRT: 0.5 (0.2; 0.8); PRT: -0.0 (-0.3; 0.2), p=0.02]. HC improved TMV of the knee extensors and flexors, respectively [non-PRT: -74.9 (-219.9; 70.0) vs. PRT: 110.0 (59.6; 160.4)]; [non-PRT: -7.6 (-71.9; 56.8) vs. PRT: 91.7 (51.6; 131.8)] and FF of the knee extensors [non-PRT: 1.100 (0.39; 1.81) vs. PRT: 0.09 (-0.09; 0.28), $p<0.05$ for all]. No improvements for TMV and FF were found in individuals with DPN.

Conclusions:
PRT resulted in muscle strength gains of the knee extensors and flexors in all groups. However, TMV and FF only improved in HC and in individuals with diabetes without DPN, while no improvements were found in individuals with DPN. These findings indicate that individuals with DPN improve their muscle strength without post exercise hypertrophic adaptations.

References:
Yes

References 1:
Khan KS, Overgaard K, Tankisi H, Karlsson P, Devantier L, Gregersen S, Jensen TS, Finnerup NB, Pop-Busui R, Dalgas U, Andersen H. Effects of progressive resistance training in individuals with type 2 diabetic polyneuropathy: a randomised assessor-blinded

References 2:
Stouge A, Khan KS, Kristensen AG, Tankisi H, Schlaffke L, Froeling M, Væggemose M, Andersen H. MRI of Skeletal Muscles in Participants with Type 2 Diabetes with or without Diabetic Polyneuropathy. Radiology. 2020 Dec;297(3):608-619. doi: 10.1148/radiol.20

References 3:

References 4:

Grant Support:

Keywords: Training, MRI, Diabetic polyneuropathy, Hypertrophic adaptations

Treatment-induced Neuropathy Of Diabetes Is Rare In a Tertiary Diabetes Centre – A Preliminary Analysis

Poster No:
P 229

Authors:
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Institutions:
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Introduction:
Treatment-induced neuropathy of diabetes (TIND) is an uncommon acute, painful small-fibre and autonomic neuropathy following rapid glycemic improvement in patients with long-standing hyperglycemia. Prevalence was reportedly up to 10.9% among patients referred to tertiary neuropathy clinics. The incidence in general diabetes mellitus (DM) clinics is uncertain. Our primary hypothesis is that TIND incidence is low in these context.

Methods:
We conducted a prospective nested case-control study in a diabetes centre and included DM patients with recent HbA1c drop of at least 2% in 3 months. These patients were interviewed at 4, 8 and 12 week intervals to identify neuropathic and/or autonomic symptoms suggestive of TIND; and corroborated with questionnaires (MNSI, COMPASS-31 and Likert scale). Patients who developed symptoms ('cases') and age-matched controls underwent continuous glucose monitoring, autonomic (TM-flow) and neuropathic assessments (neurothesiometer, monofilament and thermal thresholds) and retinal imaging at diagnosis and 1 year.

Results:
One hundred patients have been recruited. Mean age is 51(22-77) years, 65 females. All except 3 patients have type 2 DM with a mean duration of 8.2(0-40) years. Twenty-three patients have at least 1 microvascular complication. Median HbA1c decline is 4.6(2.0-11.6)% over 2.5 months. Eighty-seven patients have completed the 12-week follow-up period. Only 5 patients have symptoms suggestive of TIND in this epoch; one with neuropathic pain and autonomic symptoms, while the rest had only autonomic symptoms. 4 of 5 patients have retinopathy; of whom 2 also have maculopathy. Comparing cases to controls, age, gender and DM types were similar, while median initial HbA1c prior to rapid decline was the same at 12.5%.

Conclusions:
Our preliminary analysis suggests that TIND incidence is likely low in a general DM clinics. Recruitment is ongoing. Longitudinal follow-up and comparison of the phenotypic and glycemic characteristics between cases and controls will improve our understanding of risk factors underlying the development of TIND.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Neuropathic pain, Autonomic dysfunction, Insulin neuritis, TIND, Diabetes mellitus

Glycemic Variability and Corneal Nerve Imaging in Treatment-Induced Neuropathy of Diabetes – Preliminary Analysis

Poster No:
P 230

Authors:
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Institutions:
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Introduction:
We hypothesize that high glycemic variability (GV) in addition to rapid glycemic improvement predisposes to development of an acute painful autonomic neuropathy, treatment-induced neuropathy of diabetes (TIND).

Methods:
We prospectively recruited patients with HbA1c 9% or more from outpatient Endocrine clinics at tertiary hospitals and prospectively followed them for 6 months for development of TIND. Rapid glycemic improvement is defined by HbA1c drop of at least 4% in 6 months(or equivalent). GV (Coefficient of Variation (CV) and Mean Amplitude of Glycemic Excursions (MAGE)) is calculated from continuous glucose monitoring using Libre Pro sensors. We assessed small fibre and autonomic functions at baseline and 6 months with questionnaires (DN4, UENS, COMPASS-31), cardiovascular/sudomotor autonomic reflex tests and corneal nerve imaging. Demographics, clinical features, glycemic profiles, including CV and MAGE, autonomic functions and corneal innervations are compared between those with rapid glycemic improvement and development of TIND symptoms, against those without a rapid decline in HBA1c within this 6-month epoch.

Results:
Twenty-two patients have been recruited (median age 50 years, 12 males); all T2DM with median disease duration of 17 years. Median HbA1c is 9.6% with CV and MAGE at 32.7% and 9.1mmol/l respectively. 54.5% have pre-existing microvascular complication. Of these, only 2 have clinical features of peripheral neuropathy, 1 abnormal heart rate variability and 2 abnormal sudomotor function. On the other hand, corneal nerve fibre length and fractal dimensions are decreased in all patients. Corneal inflammatory cells appear similar with controls.

Conclusions:
Glycemic variability is high in this cohort with poorly controlled T2DM. Although only 2 patients each have peripheral neuropathy or abnormal autonomic function using standard clinical evaluation, corneal denervation is seen in all patients. Ongoing recruitment and follow-up assessments will expand our understanding of glycemic variability in TIND, and discern the utility of autonomic testing and corneal imaging in TIND diagnosis.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: TIND, Insulin neuritis, Corneal confocal microscopy, Diabetes mellitus, Small-fibre

Pre-diabetic small fiber neuropathy: a murine in vitro model

Poster No:
P 231

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Introduction:
Small fiber neuropathy (SFN) results from A-delta and C-nerve fiber impairment. Diabetes is a common cause of SFN, however, the association between pre-diabetes and SFN is hardly studied. We aimed to establish a murine in vitro hyperglycemia model to investigate the mechanisms underlying SFN in pre-diabetes.

Methods:
Murine neuron cultures obtained from the dorsal root ganglia (DRG) of C57BL/6 mice were incubated with defined glucose concentrations (17 mM = normoglycemia, 45 mM or 60 mM = hyperglycemia) for 24h. To assess glucose effects, we assayed reactive oxygen species (ROS) as oxidative stress marker. We investigated protein and gene expression of superoxid-dismutase (SOD)2, caspase-3, and interleukin (IL)-6 as markers for analyzing ROS expression, apoptosis, and inflammation via immunocytochemistry and quantitative real-time PCR.

Results:
In DRG cultures incubated with 60 mM glucose, median ROS intensity was higher compared to neurons incubated in 17 mM glucose ($p<0.001$). Median intensity level of SOD2, which controls ROS expression, was lower in hyperglycemic than in normoglycemic DRG cultures (45 mM vs. 17 mM: $p<0.05$; 60 mM vs. 17 mM: $p<0.001$). We confirmed these results on gene expression levels (60 mM vs. 17 mM: $p<0.001$) and further found lower numbers of SOD2 expressing DRG neurons incubated with 60 mM compared to 17 mM glucose ($p<0.001$). We also found a higher median caspase-3 intensity and number of caspase-3 positive neurons upon incubation with 60 mM compared to 17 mM glucose ($p<0.001$, each). Despite alterations in apoptosis and stress markers, we found no intergroup difference for IL-6 as an inflammatory marker.

Conclusions:
We have validated a hyperglycemic murine in vitro model and have developed a tool to study morphological and functional effects of hyperglycemia on sensory neurons. Our model may enable the investigation of mechanisms underlying early development of SFN in pre-diabetes and provide targets for prevention.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: small fiber neuropathy, pre-diabetes

Distal Symmetric Polyneuropathy Prevalence and Predictors in a Population-based Household Survey in Urban and Rural Zambia

Poster No:
P 232

Authors:
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Introduction:
Studies in Zambia and Uganda have reported very high (11-12%) prevalence of distal symmetric polyneuropathy (DSP) in HIV negative populations, but little is known about DSP outside of clinical settings. This study evaluates DSP prevalence and predictors in Zambian communities to guide future interventions.

Methods:
Using a household survey in one urban and one rural district, adults (≥18 years) were examined and interviewed about DSP, sociodemographic and medical characteristics, food security, and alcohol intake. DSP was defined as ≥1 bilateral symptom (pain, numbness, paresthesias) and ≥1 bilateral sign (diminished/absent distal pin and/or vibration sensation, or reflexes) using the Brief Peripheral Neuropathy and Utah Early Neuropathy Scales. HIV testing was also provided.

Results:
Among 445 households, 1161 adults were examined (62% female; median age 35 [IQR 24-50] years). DSP prevalence was 13.3% (n=154; 95% CI 11-15%) and did not differ by urbanicity. DSP cases were more likely to be female (71% versus 61%; p<0.01), were older (median age 56.5 versus 32 years; p<0.00001), had less education (mean 6.3 versus 8.4 years; p<0.0001), and were more food insecure (30.5% versus 19.6%; p=0.002). Among 913 (78.6%) participants with known HIV status, DSP cases were more likely to be HIV positive (36.1% versus 20.4%; p<0.0001), have prior tuberculosis treatment (n=12.3% versus n=5.3%; p=0.001), and have diabetes (7.1% versus 1.3%; p<0.0001). There was no association with alcohol intake (p=0.48). In a multivariable logistic regression model, age (OR 1.05; 95% CI 1.03-1.06), food insecurity (OR 1.93; 95% CI 1.22-3.05), HIV (OR 1.8;1.12-2.86), and diabetes (OR 4.2; 1.42-12.7) remained significant DSP predictors (p<0.00001).

Conclusions:
DSP is present in >1 in 10 adults in Zambia. Community health worker engagement should be investigated to identify DSP cases and screen for HIV and diabetes, and to consider nutritional/dietary interventions that may reduce DSP and other associated noncommunicable diseases morbidity and mortality through early intervention.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: National Institute of Neurological Disorders & Stroke (Award Number K23NS117310)
Allen Foundation Award

Keywords: Global Health, Epidemiology, Distal Symmetric Polyneuropathy, HIV, diabetes

The Critical Need for a DPM and PT Collaborative Approach to Fall Prevention in Patients with Diabetes, with AND without diagnosed Neuropathy

Poster No:
P 233

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Introduction:
Falls are a healthcare challenge in the United States, costing more than $30 billion annually. Patients with diabetes have a greater risk of falls and fall related injuries than non-diabetics due to numerous factors, including; peripheral neuropathy, peripheral arterial disease, impaired postural control, altered gait patterns, sarcopenia, and other co-morbidities. Numerous studies have demonstrated the importance of early risk detection and prevention interventions. Despite the significant risk, cost, morbidity, mortality, and negative impact on quality of life, referral for balance assessment in diabetic patients is not common. This retrospective analysis identifies the potential benefit of a collaborative approach between Podiatrists and Physical Therapists in identifying those at risk.

Methods:
43 diabetic patients (mean age 58.7 years, mean diabetic age 7.5 years, 32 females) seen for an outpatient podiatry visit were later assessed by physical therapists using patient reported, functional, and clinical outcome measures and tests, along with a patient questionnaire.

Results:
100% of patients were never previously referred for balance testing, 26% reported neuropathic symptoms, 41% reported at least one fall in the past 12 months, and 19% used an assistive device. 37/43 patients agreed to clinical and functional testing and 90% of patients who did not report neuropathic symptoms, demonstrated an increased risk of falling.

Conclusions:
A collaborative approach between podiatrists and physical therapists aimed to identify and prevent falls in a diabetic population is feasible and can identify patients at risk, even in patients not diagnosed with, nor report neuropathic symptoms. Changing the standard of practice for primary care providers, endocrinologists, and podiatrists to include referral to physical therapy for diabetic patients may help to identify patients for whom skilled intervention is warranted. This change may help earlier initiation of tailor made interventions to reduce falls risk, save healthcare costs, enhance patient function, and improve quality of life.

References:
Yes

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References 2:

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Test -retest reliability, internal consistency, construct validity and factor structure of a falls risk perception questionnaire in older adults with type 2 diabetes mellitus: a prospective study Janelle Gravesande et al Arch Physiother 2019 Dec2;9:14

Grant Support:

Keywords: collaboration, fall risk, physical therapy, podiatry, outcome measures

ALTERATIONS IN EPIDERMAL CELLS AND APPENDAGES IN PERIPHERAL NEUROPATHY

Poster No:
P 234

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Introduction:
Punch skin biopsy is a useful technique to evaluate peripheral neuropathy by providing an objective measurement of small unmyelinated nerve fibers. Focus has concentrated on quantification of intraepidermal nerve fiber density (IENFD) while epidermal cells and skin appendages that support epidermal nerves and/or components of specialized sensory complexes have been relatively under investigated. Here, we describe the distribution of several epidermal structures including Merkel cells (MCs), Langerhans cells and a population of heterogeneous cells expressing the neuronal marker, class III β-tubulin (Tuj1), in normal healthy subjects and patients diagnosed with peripheral neuropathy (PN) associated with either HIV (HIVPN) or type 2 diabetes (DPN).

Methods:
Three mm punch skin biopsies were obtained. Fifty um skin sections were processed for immunohistochemistry using several markers including PGP9.5, cytokeratin 20, Tuj1, CD1a and Melan-A. Structures were quantified using stereology or validated quantification methods.

Results:
The distribution of MC in healthy controls was patchy and followed a proximal: distal gradient along the leg, similar to IENFD. MC density was reduced in PN subjects with a more patchy distribution. Tuj1 expressing cells possess dendritic-like processes and typically have a bipolar appearance and often were closely juxtaposed to epidermal axons, suggesting a functional interaction. The Tuj1 positive cells were distributed homogenously along the basal epidermal layer and also displayed a proximal > distal leg gradient. The majority Tuj1+ cells are immunoreactive for Melan-A, a melanocyte marker. When compared to healthy controls, patients with HIVPN or DPN showed significant reductions in Tuj1+ cells ($p<0.01$). However, the density of Melan-A + cells was comparable between normal controls and the PN patients, indicating reduced expression of Tuj1 rather than a cell loss.

Conclusions:
Further characterization these cells might help to understand the processes and mechanisms of peripheral neuropathy, which could be potentially used as novel measures to increase the diagnostic yield of skin biopsy.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: punch skin biopsy , peripheral neuropathy , Merkel cells , class III β-tubulin , Melan-A

Is diabetic papillopathy a complication of rapid glycaemic control?

Poster No:
P 235

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Institutions:
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Introduction:
We hypothesize that diabetic papillopathy lies in the spectrum of neurological complications following rapid glycaemic control, such as treatment induced neuropathy of diabetes mellitus (TIND).

Methods:
We report 3 cases of diabetic papillopathy seen at a tertiary eye care institute in Singapore. Diabetic papillopathy was defined as unilateral or bilateral optic disc swelling in patients with diabetes mellitus (DM), with nil or mild optic nerve dysfunction and exclusion of other causes including non arteritic ischemic optic neuropathy.

Results:
Of the 3 patients, 2 were asymptomatic while 1 presented with bilateral blurring of vision over 3 weeks. The patient's age range was 48 to 69 years. 2 were females and 1 male. All 3 patients had type 2 DM. Median duration of DM was 7 years (range was 4 months to 15 years). 2 patients were on insulin, while all 3 were on oral hypoglycaemic agents. 2 had severe and 1 had mild non proliferative diabetic retinopathy. 1 patient had diabetic nephropathy. Contemporaneous to the development of diabetic papillopathy, the median change in HbA1c was 3.4% over 4 months (range 1.6% to 8%). The HbA1c decrease per month was 0.4%, 0.8% and 2% respectively. At least 1 patient had documented symptomatic hypoglycemia. When diabetic papilopathy was diagnosed, none of the patients had acute maculopathy or documented symptoms of painful small fibre neuropathy or autonomic dysfunction. 2 patients improved clinically while the 3rd is pending followup.

Conclusions:
Vasculopathy from acute endothelial dysfunction is believed to be the pathophysiological mechanism of tissue injury in TIND. We speculate that optic nerve head ischemia which overlaps with non arteritic ischemic optic neuropathy could play an important part in the development of diabetic papillopathy. This preliminary observation has prompted us to further explore the putative link between rapid glycaemic control and diabetic papillopathy through retrospective and prospective case series.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Diabetes Mellitus , Diabetic papillopathy, Treatment-induced neuropathy of diabetes

Patient-reported Impact Of Guillain-Barré Syndrome (GBS) Based On The (Rasch-)Fatigue Severity Scale

Poster No:
P 236

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Introduction:
The Fatigue Severity Scale (FSS) and the Rasch-built Fatigue Severity Scale (R-FSS) are commonly used patient-reported outcome measures (PROMs) in patients with immune-mediated neuropathies that assess the impact and severity of fatigue. Fatigue is considered one of the most disabling symptoms and is already present during the early stage of GBS. The present study aimed to describe the impact of fatigue in patients with GBS. In addition, we aim to further validate the (R-)FSS in GBS since not all measurement properties have yet been assessed.

Methods:
This study was based on prospective observational data from the International GBS Outcome Study (IGOS) and IGOS Zika. The FSS consists of 9 items, which are scored on a 7-point Likert scale with scores ranging from 9 to 63. The R-FSS consists of 7 items which are scored on a 4-point Likert scale with scores ranging from 0 to 21. Higher scores on both the R-FSS and FSS indicate greater fatigue. Median (R-)FSS scores (IQR) were calculated at 26 weeks follow-up. Structural validity, internal consistency, construct validity, and cross-cultural validity were assessed.

Results:
Median FSS scores (IQR) vary across regions ($p < .001$) with the highest score in European (35 [17-49]) and North-American patients (31 [16-48]). Lower scores were reported by patients from Asia (11 [9-27]), Bangladesh (18 [9-33]) and South-Africa/Argentina/Australia/Brazil (10 [9-28]). Regarding clinical variants, median FSS scores (IQR) were the highest in patients with sensorimotor GBS (28 [11-45]). Lower scores were reported by patients with pure motor (20 [9-42]), Miller Fisher(-overlap) syndrome (21 [9-40]) and other variants including pharyngeal-cervical-brachial weakness, pure sensory and the ataxic form (23 [9-48]). The distribution of FSS scores varies in different GBS variants ($p = .01$).

Conclusions:
Further detailed Rasch based analyses of both the FSS and R-FSS are ongoing, and these results will be presented at the upcoming PNS meeting.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: The Fatigue Severity Scale (FSS)

Cardiovascular autonomic neuropathy in patients with type 2 diabetes with and without sensorimotor polyneuropathy

Poster No:
P 237

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Introduction:
Cardiovascular autonomic neuropathy (CAN) in patients with diabetes is associated with a poor prognosis. We aimed to assess the prevalence of autonomic symptoms and signs of CAN among type 2 diabetes patients with and without sensorimotor polyneuropathy (DPN and noDPN) and healthy controls (HC). Secondarily, we aimed to describe the characteristics of subjects with CAN.

Methods:
We included patients from the Danish Centre for Strategic Research in Type 2 Diabetes (DD2) cohort. DPN was defined according to the Toronto classification. Subjects were examined with the Vagus™ device and modified Schellong test for the diagnosis of CAN where one abnormal cardiovascular autonomic reflex test (CART) indicates possible CAN, two or more abnormal tests indicate definite CAN, and the additional finding of orthostatic hypotension indicates advanced CAN. Autonomic symptoms were assessed with the Composite Autonomic Symptom Score 31 (COMPASS 31) questionnaire.

Results:
Of 277 subjects with diabetes, 214 had DPN, and 63 had noDPN. We included 97 HC. The prevalence of definite CAN was 22%, 7% and 3% in DPN, noDPN and HC respectively. COMPASS 31 scores were higher in patients with DPN compared to noDPN (20.0 vs 8.3). Patients with definite CAN reported more autonomic symptoms than subjects with possible CAN and no CAN (22.1 vs 11.7 vs 12.3). Patients with CAN were younger, had a higher BMI, most often had DPN and their biochemical profile was characterized by higher HbA1c and higher triglycerides.

Conclusions:
In this cohort of type 2 diabetes patients 1 in 5 with DPN had definite CAN and almost all patients with definite CAN had DPN. Autonomic symptoms were more common in patients with DPN than noDPN as well as with definite CAN compared to no CAN.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Diabetes, Autonomic, Neuropathy, CAN, COMPASS31

Treatment Induced Diabetic Lumbosacral Radiculoplexus Neuropathy

Poster No:
P 238

Authors:
Marcus Pinto[1], Catarina Aragon Pinto[1], Kamal Shouman[1], Pannathat Soontrapa[2], Hebatallah Rashed[1], Michelle Mauermann[1], Sarah Berini[1], Phillip Low[1], Christopher Klein[1], Peter Dyck[1], P. James B. Dyck[1]

Institutions:
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Introduction:
Treatment induced diabetic neuropathy (TIND) is a painful, autonomic neuropathy occurring after rapid hyperglycemic correction. We investigate whether rapid hyperglycemia correction can trigger diabetic lumbosacral radiculoplexus neuropathy (DLRPN)

Methods:
DLRPN cases were retrospectively identified from January 1st 2000 to December 31st 2018. Included cases had diabetes and lower limb pain, numbness or weakness and EMG abnormality of at least 2 peripheral nerves and 2 nerve root levels. All cases had HbA1C history available and had autonomic reflex screen, and EMG performed. Treatment induced DLRPN (TI-DLRPN) was defined by DLRPN onset within 8 weeks of a decrease in HbA1C of ≥2% points over 3 months.

Results:
158 DLRPN patients were included. Median age was 65 years (range 26-84) and 64% (101/159) were male. 20% (31/158) had TI-DLRPN. Of TI-DLRPN, 97% had weakness (30/31), 94% paresthesias (29/31), 61% autonomic symptoms (19/31), 97% neuropathic pain (30/31), and 55% contact allodynia (17/31). 97% (30/31) had type 2 DM, median modified Rankin score was 4 (1-5) and 97% had abnormal autonomic testing (CASS ≥ 1)(30/31). The median HbA1c change associated with TI-DLRPN was 5% (2.1-8.8). TI-DLRPN patients were younger (median 58 years [36-77] vs 66 [26-84]; p= 0.0345), had higher CASS scores (median 5 [0-9] vs 3 [0-10]; p= 0.0046], and more frequently used insulin (55% [17/31] vs 28% [35/125]; p= 0.0056) compared to other DLRPN patients. Other demographic variables, HbA1c, fasting glucose, autonomic, motor, and sensory symptoms, and level of impairment were similar between groups.

Conclusions:
Rapid hyperglycemia correction triggered DLRPN in 20% of cases. TI-DLRPN has more severe autonomic impairment but otherwise has similar clinical features to usual DLRPN. Herein we demonstrate that DLRPN can be a form of treatment induced diabetic neuropathy with subacute pain and autonomic impairments like TIND but unlike TIND usually occurring in type 2 DM with weakness.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Diabetes mellitus, Diabetic lumbosacral radiculoplexus neuropathy, Treatment induced neuropathy of diabetes

Triggers for Lumbosacral Radiculoplexus Neuropathy

Poster No:
P 239

Authors:
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Institutions:
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Introduction:
To investigate potential triggers for Lumbosacral Radiculoplexus Neuropathy (LRPN), both diabetic (DLRPN) and non-diabetic (NDLRPN).

Methods:
LRPN cases were retrospectively identified from 1/2000 to 12/2018. Included cases had lower limb pain, numbness or weakness and EMG abnormality of at least 2 peripheral nerves from 2 nerve root levels. Included cases had EMG performed and were seen by neuromuscular neurologists. Neuropathy triggers were defined as time-related events before LRPN onset.

Results:
357 patients were included. Median age was 65 years (range:19-94) and 62% (222/357) were male. 259 patients had DLRPN (72.5%) and 98 NDLRPN (27.5%). Triggers for LRPN were found in 58% (208/357). The most common trigger was a new exercise regimen and/or diet change 49% (102/209) , followed by surgery (37%, 77/208), infection (21%,43/208), intensive glucose control (15%,31/208), unintentional weight loss (> 10 lbs) secondary to poor diabetic-control or systemic illness (11%,22/208), trauma (3%,6/208) and vaccination (3%,6/208). Among patients whose trigger was a new exercise regimen/diet change, 89% (91/102) had > 10 lbs. intentional weight loss. In LRPN with an associated trigger, 34% (72/209) had more than 1 potential trigger. LRPN patients with a trigger had more frequent weight loss (> 10 lbs.) than patients without triggers (78% vs 49%; $p < 0.0001$). Triggers were more common in patients with DLRPN than NDLRPN (66% vs 40%,$p < 0.0001$).

Conclusions:
LRPN may be induced by a trigger in almost 60%. Associated triggers occur in other monophasic immune mediated neuropathies (AIDP and inflammatory brachial plexopathy). Weight loss (intentional or unintentional) and increased exercise/rapid hyperglycemia correction appear to be the most important triggers for LRPN, followed by surgery and infection. These data raise the possibility that LRPN is more common in diabetes partly because of the more profound metabolic changes accompanying weight loss, rapid correction of hyperglycemia and exercise in these individuals.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Diabetes mellitus, Diabetic lumbosacral radiculoplexus neuropathy, Non-diabetic lumbosacral radiculoplexus neuropathy, triggers

The growth modulatory effects of the Myc/Max/Mad1 signaling network in the regenerating peripheral nervous system.

Poster No:
P 240

Authors:
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Introduction:
The regenerative competency of the PNS suggests that axonal damage from neuropathy or trauma is associated with robust functional recovery. However, patients with axonal damage can be left with debilitating and life-long impairments, greatly impacting their quality of life. Molecular strategies that manipulate intrinsic growth properties of neurons may offer therapeutic targets to enhance regenerative recovery. Here, we investigated the Myc/Max/Mad1 signaling axis and its influence in the regrowing PNS.

Methods:
Adult sensory neuron cell culture. siRNA, CRISPR knockdown. Sciatic crush injury model in mice with regeneration indices.

Results:
Myc/Mad/Max were expressed in the PNS, and were injury responsive. Two separate Mad1 targeted siRNAs, or a CRISPR plasmid containing a Mad1 targeting sequence, bolstered the growth response of injured DRG neurons. We further targeted two Myc family members (c-/N-Myc) or Max to evaluate their impact on regrowing neurons in vitro. Isolated knockdown of either Myc isoform had no effect on growth, however combined knockdown of both isoforms simultaneously blunted growth. The small inhibitor molecule 10058-F4, to simultaneously block both Myc isoforms, resulted in a dose dependent reduction in neuron growth in vitro. Unexpectedly Max knockdown also improved neurite outgrowth, suggesting an inhibitory role in the PNS. Finally, using a sciatic crush nerve injury model, we investigated the impact of blinded, near injury injections of Mad1 siRNA . A month following the first injection of siRNA, we noted improved electrophysiological, behavioral, and histological indices of regeneration associated with Mad1 siRNA compared to animals receiving scrambled sequence controls.

Conclusions:
Overall, these data present Myc as a potent accelerator of growth, while Mad1 and Max function as barriers for robust functional recovery, offering novel therapeutic targets.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: Canadian Institutes of Health Research

Keywords: axon regeneration, Myc signaling, sensory neuron plasticity, Mad1

Ischemic injury and microvasculitis in Treatment Induced Neuropathy of Diabetes

Poster No:
P 241

Authors:
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Institutions:
[1]Mayo Clinic, Rochester, MN, [2]Federal University of Rio de Janeiro, Rio de Janeiro, RJ, [3]Mayo clinic, Rochester, MN, [4]Mayo clinic, Rochester , MN

Introduction:
Treatment induced neuropathy of diabetes (TIND) is a painful, autonomic, subacute neuropathy occurring after rapid hyperglycemia correction, usually in type 1 diabetes (DM). The pathophysiology of TIND is not well understood. Diabetic lumbosacral radiculoplexus neuropathy (DLRPN) is also a panful, subacute neuropathy mostly of type 2 DM that is due to ischemic injury and microvasculitis. We postulate that some cases of TIND may also be due to ischemic injury and microvasculitis.

Methods:
We retrospectively identified TIND patients seen at our institution who had undergone nerve biopsy between 2004 - 2022. TIND was defined as acute neuropathic pain and/or autonomic impairment within 8 weeks of marked improvement in glycemic control in DM (decrease in HbA1c of 2% over 3 months). Clinical, electrophysiological and pathological characteristics were collected.

Results:
Six TIND patients with nerve biopsies were identified. All were males, and median age was 57.7 years (range 45-70). All had neuropathic pain, 5 had autonomic symptoms, and 3 had paresthesias. Neurological examination showed decreased pinprick and temperature in the feet with normal strength in all. All biopsies had perivascular inflammatory infiltrates (large [3], moderate [1] and small [2]); 2 were diagnostic and 2 others highly suggestive of microvasculitis. Four biopsies showed evidence of ischemic injury: multifocal fiber loss (3), neovascularization (3) and perineurial thickening (3). On teased fibers, there was increased axonal degeneration (mean 19.6%; 3-60%) with some secondary segmental demyelination (mean 3%; 0-8.3%).

Conclusions:
Our findings suggest that ischemic injury and microvasculitis may be the putative mechanism of TIND (4 of 6 biopsies showed microvasculitis). The pathological findings are similar to DLRPN. We postulate that the rapid hyperglycemia correction triggers an immune attack on nerves (as can also occur in DLRPN). Larger studies are needed to confirm microvasculitis as the main pathology of TIND.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Diabetes, neuropathy, TIND, Inflammation, Pathology

Effect of B Vitamins on Neurite Regeneration in a 3D Co-culture Model of Neurodegeneration

Poster No:
P 242

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Introduction:
Peripheral neuropathy (PN) is the most common disorder of the peripheral nervous system in adults caused by different aetiologies with diabetes as the most common cause [1,2]. Diabetic peripheral neuropathy (DPN), affecting 50% of adult diabetics, results in pain, paraesthesia, and sensory loss, negatively impacting quality of life [3]. There are currently no pharmacological treatments to reverse DPN [4]. The neurotropic B vitamins (B1, B6 and B12) play an essential role in the health of the nervous system and have therefore been suggested to have the potential to treat PN. The aim of our study was to determine the regenerative capacity of vitamin B1, B6 and B12 following neurite degeneration *in vitro* and explore the mechanisms through which these effects occur.

Methods:
Following the development of a novel 3D-engineered co-culture degeneration model, we tested the regenerative capacity of vitamin B1 (thiamine hydrochloride), B6 (pyridoxal hydrochloride) and B12 (cyanocobalamin). This involved seeding NG108-15 cells on top of a collagen matrix containing SCL4.1/F7 Schwann cells which were then insulted with hydrogen peroxide to induce degeneration. Neurite length was analysed using βIII-Tubulin immunostaining.

Results:
Treatment with B vitamins; B1, B6 and B12 individually or in combination were found to extend neurite length significantly in comparison to a no treatment control. This significantly beneficial effect on neurite extension was seen with both pre- and post-insult vitamin B treatment.

Conclusions:
In conclusion, we have established a novel model of neurodegeneration which can be used to explore the neuromodulatory effects of compounds. This study provides evidence that the B vitamins have a beneficial neurite regenerative effect *in vitro*. Further *in vitro* assays exploring metabolism and cell phenotype are currently being conducted to decipher the mechanistic effects of these B vitamins.

References:
Yes

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Grant Support:

Keywords: Peripheral neuropathy, B vitamins, In vitro model

Autonomic Neuropathy in Diabetic and Nondiabetic Lumbosacral Radiculoplexus Neuropathy; comparison to CIDP

Poster No:
P 243

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Introduction:
To describe autonomic symptoms and findings in a large cohort of diabetic and non-diabetic lumbosacral radiculoplexus neuropathy (DLRPN and NDLRPN) and compare the autonomic involvement of LRPN and CIDP.

Methods:
DLRPN, NDLRPN, and CIDP cases were identified through a retrospective review (1/2000 to 12/2018). LRPN had lower limb predominant neuropathy with pain, numbness, or weakness with EMG involvement of at least 2 peripheral nerve and 2 nerve root levels. Structural causes were excluded. CIDP was defined by 2021 PNS criteria. All included cases had autonomic reflex screen and EMG.

Results:
234 cases of DLRPN, 94 cases of NDLRPN, and 91 cases of CIDP were included. At autonomic testing, median ages were: DLRPN 65 years (range: 23-83), NDLRPN 68 years (19-94) and CIDP 50 years (11-87). 64 % (149/234) of DLRPN, 54% (51/94) NDLRPN and 54% (49/91) CIDP were male. Autonomic symptoms (DLRPN vs. NDLRPN) (47% vs 33%; p= 0.0159) and impairment (CASS $\geq$ 1; 91% vs 78%; p= 0.0052; median CASS scores: 4 [0-10] vs. 2 [0-8]; p < 0.0001) were common in both groups and more frequent and severe in DLRPN than in NDLRPN. Compared to CIDP, LRPN (DLRPN and NDLRPN) had more frequent autonomic symptoms (43% vs 21%; p<0.0001) and impairment (87% vs 49%; p<0.0001) and these were more severe [median CASS score: 3 (0-10) vs 0 (0-10); p<0.0001].

Conclusions:
Autonomic neuropathy is common in both DLRPN and NDLRPN, but more frequent and severe in DLRPN; this suggests that both metabolic derangement from diabetes mellitus and microvasculitis from LRPN are pathophysiologically important in the observed autonomic dysfunction. The more frequent and severe autonomic neuropathy of LRPN compared to CIDP underscores the different underlying pathologies of these inflammatory neuropathies and is helpful in separating them.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: autonomic dysfunction, diabetic lumbosacral radiculoplexus neuropathy, non-diabetic lumbosacral radiculoplexus neuropathy, CIDP

Cystatin C is Associated With Signs of Early Neuropathy in a Population of Older Adults

Poster No:
P 244

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Introduction:
Peripheral neuropathy in older adults is frequent and underdiagnosed, multifactorial or idiopathic. Serum cystatin C (CysC), a cysteine protease inhibitor produced by nucleated cells, is presented as an independent risk factor for early kidney disease, biomarker in diabetic complications, of inflammation and of degenerating neurons. Our aim was to study an association between CystC and early neuropathy in lower extremities of older adults.

Methods:
Two age cohorts from a swedish, community-dwelling, population study were examined according to the Utah Early Neuropathy Scale (UENS)(score: 0—42), an instrument developed to measure peripheral nerve function weighted toward signs typical in early polyneuropathy. Serum CysC levels were measured and medical examination was performed. Cohort-1 included 900 younger elderly 65—79y (mean age 69.6; SD 4.3), and cohort-2 with 581 oldest-old participants 80—102 yrs (mean age 83.6; SD 3.4)

Results:
Mean UENS score in Cohort-1 was 3.8 (SD 2.9) and in Cohort-2: 7.6 (SD 6.1), while mean CysC was 1.01 mg/L (SD 0.25) and 1.33 mg/L (SD 0.43) respectively. Using linear regression analysis with UENS as dependent variable, we calculated an association with CysC after adjusting for: age, diabetes mellitus, treatment of hypertension, BMI, active/former smoking, and frequency of alcohol consumption. We observed in Male subjects in Cohort-1 (n=459) a significant association between UENS and CysC (β= 2.28, 95%CI: 1.02—3.54; p=0.0004), but not in Female subjects (n=441) (β= -0.005, 95%CI: -1.05—1.04; p=0.99). In Cohort-2, UENS score was also associated with CysC only in Male subjects (n=261)(β=2.62, 95%CI: 0.65—4.60; p=0.01), but not in Females (n=320) (β= 1.93, 95%CI: 0.10—3.95; p=0.06). UENS scores were not associated with serum creatinine levels.

Conclusions:
In a general population of elderly 65-79 and 80-102 years, signs of early neuropathy in lower extremities estimated with UENS scale are independently associated with levels of Cystatin C in male subjects suggesting vascular mechanism of peripheral nerve degeneration.

References:
Yes

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Grant Support: The Swedish Ministry of Health and Social Affairs, the Skåne Regional Council, and the Swedish Medical Research Council no. 2017-01613; 2017-00639.

Keywords: Cystatin C, UTAH early neuropathy scale, older adults, population study, biomarkers

Advanced Glycation End-Products as Serum Biomarkers for Diabetic Peripheral Neuropathy in Type 1 Diabetes

Poster No:
P 245

Authors:
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Introduction:
The aim of this study was to investigate the potential of advanced glycation end-products (AGEs) as serum biomarkers for diabetic peripheral neuropathy (DPN) in type 1 diabetes mellitus (T1DM).

Methods:
Participants were divided into four well-characterized groups: healthy controls; T1DM; T1DM with non-painful DPN; and T1DM with painful DPN. Group placement was determined using the Toronto consensus criteria for DPN. Blood samples were analyzed for dicarbonyls and biomarkers of glycation, oxidation and nitration.

Results:
The results of the statistical analysis, before adjusting for confounders, revealed that 11 out of the 13 investigated biomarkers (84.6%) had significant differences in serum levels between all groups ($P<0.05$). After adjusting for sex, age, HbA1c levels, and diabetes duration, 9 out of 13 biomarkers (69.2%) showed significant differences ($P<0.05$). The biomarker levels that were found to be different included the AGEs MG-H1, G-H1, CML, fructosyl-lysine and glucosepane, the oxidation biomarker methionine sulfoxide, the nitration biomarker 3-nitrotyrosine, and the dicarbonyls methylglyoxal and 3-deoxyglucosone. To identify specific biomarkers associated with DPN (non-painful and painful), odds ratios (OR) on standardized biomarker values were generated and adjusted for confounders. The control group was not included in the OR analysis. A significant increase in OR for DPN was observed in 3 out of the 9 biomarkers (33.3%). These included the AGEs G-H1 (OR=1.91, P=0.008), and glucosepane (OR=2.05, P=0.036), and the nitration biomarker 3-nitrotyrosine (OR=2.59, P=0.014). A mean of all standardized AGE-values revealed an increase in the OR for DPN (OR=3.86, P=0.010).

Conclusions:
In conclusion, this study found that AGEs were associated with DPN, possibly suggesting a central role of AGEs and nitration in the development of DPN in individuals with T1DM. Specifically, the AGE biomarkers G-H1 and Glucosepane, and the nitration biomarker 3-nitrotyrosine, as well as mean AGE-values showed an association with DPN in T1DM.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: This study is supported by a grant from the Novo Nordisk Foundation (grant number NNF18OC0052301).

Keywords: Type 1 Diabetes Mellitus, Diabetic Peripheral Neuropathy, Advanced Glycation End-Products, Biomarkers

Effects of progressive resistance training in individuals with type 2 diabetes and pronounced motor dysfunction following diabetic polyneuropathy

Poster No:
P 246

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Institutions:
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Introduction:
Background: It remains to be studied whether individuals with type 2 diabetes (DM2) and severe diabetic polyneuropathy (DPN) including substantial muscle weakness would benefit from progressive resistance training (PRT). Aim: To assess if PRT can precipitate improved lower-body muscle strength, quality, and hypertrophy in individuals with DM2 and severe DPN.

Methods:
Methods: Participants with DM2, DPN, and a substantial reduction in muscle strength (<60% of expected muscle strength), were included. Participants underwent 12-weeks of supervised PRT following a run-in period (RP) of 12-weeks without any intervention. Primary outcomes were measures of muscle strength (peak torque) of knee and ankle extensors and flexors. Secondary outcomes included muscle volume, muscle quality (muscle strength per. muscle volume) and MRI assessment of muscle fat-infiltration. Results are presented as median-values of pooled data from proximal (knee extensors and flexors) and distal muscle groups (ankle extensors and flexors).

Results:
Results: Six male individuals (age, 69 years) with DM2 and severe DPN were included. Muscle strength (+6%, p=0.03) and lean muscle mass (+6%, p=0.04) increased at the upper-leg following PRT. Fat-infiltration increased at the upper (6%, p=0.03) and lower-leg (7%, p=0.03) in the RP. No progression of fat-infiltration was observed following PRT. Muscle quality did not change significantly through neither the RP nor PRT.

Conclusions:
Conclusion: Progressive resistance training may precipitate hypertrophy and improve muscle strength of the upper leg, and delay progression of muscle fat infiltration of the lower-body in individuals with type 2 diabetes and severe diabetic polyneuropathy.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: motor dysfunction, diabetic polyneuropathy, type 2 diabetes, progressive resistance training

The Muscarinic Receptor Antagonist Oxybutynin is a Therapeutic Candidate for Diabetic Sensory Neuropathy

Poster No:
P 248

Authors:
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Institutions:
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Introduction:
Muscarinic acetylcholine type 1 receptor (M1R) antagonism enhanced neurite outgrowth in cultured adult sensory neurons, augmented mitochondrial function in dorsal root ganglia (DRG) and prevented/reversed neuropathy in type 1 and type 2 diabetic rodents. To support rapid translation of this novel therapeutic approach to clinical trials we investigated whether oxybutynin, an antimuscarinic used to treat over-active bladder, could reverse sensory neuropathy in diabetic rodents.

Methods:
HEK293 cells were used to quantify recruitment of β-arrestin to M1R using bioluminescence resonance energy transfer (BRET). Sensory neurons were derived from DRG of control rats or streptozotocin (STZ)-induced diabetic mice and total neurite outgrowth and mitochondrial function determined. Sensory neuropathy was established in type 1 STZ-diabetic mice by testing paw thermal response latency and then oxybutynin (3-10mg/kg) applied s.c. daily for 2 months. Adult type 2 diabetic (db/db) mice received topical delivery of oxybutynin (50µl, 2%) or vehicle to the paw for 2 months followed by measurement of paw thermal response latency, collection of corneal nerve images by confocal microscopy and collection of paw skin for quantification of intraepidermal nerve fiber density.

Results:
Oxybutynin mediated β-arrestin recruitment to M1R in a concentration dependent manner and activated ERK. Cultured DRG neurons from control rats showed increased mitochondrial function in response to 100nM oxybutynin. DRG neurons from diabetic mice exhibited enhanced neurite outgrowth in response to oxybutynin (10 and 100nM). Systemic delivery of oxybutynin reversed paw thermal hypoalgesia in STZ-diabetic mice. Topical delivery of oxybutynin to db/db mice reversed thermal hypoalgesia and normalized sensory nerve density in the cornea and skin. There was no effect of oxybutynin on systemic indices of diabetes.

Conclusions:
Oxybutynin exhibits biased agonism at M1R leading to β-arrestin recruitment, activation of ERK and enhanced neurite outgrowth. This translated to reversal of functional and structural indices of sensory neuropathy in diabetic mice.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Diabetic neuropathy, Dorsal root ganglia, Muscarinic receptor, Oxybutynin, IENF

JAMAR Grip Strength is a Reasonable Surrogate Endpoint for Global Manual Muscle Strength in Peripheral Neuropathy

Poster No:
P 249

Authors:
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Institutions:
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Introduction:
Grip strength has been used for several years as a measure of muscle strength. The JAMAR dynamometer is the most widely used device for this purpose, showing good inter- and intra-rater reliability.

Methods:
From July 2018 through May 2020, 147 patients were referred for neuromuscular evaluation. All had neurologic examinations including neuropathy impairment score determinations and JAMAR grip strength measurements.

Results:
Of these 147 patients, 134 had a form of peripheral neuropathy as a final diagnosis. The remaining 13 had other non-neuropathy neurologic diagnoses. The diagnostic categories of neuropathy were length dependent sensorimotor peripheral neuropathy (LDSMPN) (n=87), small fiber neuropathy (SFPN) (n=8), sensory neuropathy (SN) (n=9), polyradiculoneuropathy (PRN) (n=5) and combinations (COMBOS) (n=25). Twenty of the 25 patients in the COMBOS category had LDSMPN. The mean neuropathy impairment score-weakness subscore (NIS-W) values [SD], paired with JAMAR grip strength values (adding left and right hand values [SD]) for each of the neuropathy subgroups were as follow: LDSMPN (3.7 [9.3],144.2 [57.3]), SFPN (0.0 [0.0], 153.2 [49.1]), SN (0.0 [0.0], 104.9 [59.4]), PRN (29.6 [25.8], 100.2 [79.0]) and COMBOS (11.2 [28.8], 117.2 [63.7]). The calculable Pearson correlation coefficients between NIS-W and JAMAR grip strength for the neuropathy subgroups (r, 95% CI, p value) were as follow: LDSMPN (r=-0.456, [-0.721, -0.074], $p<0.0001$), PRN (r=-0.667, [-0.975, 0.0523, p=0.5227) and COMBOS (r=-0.456, [-0.721, -0.074], $p<0.0001$).

Conclusions:
1. In LDSMPN, as NIS-W increases, there is a statistically significant decrease in JAMAR grip strength. 2. In LDSMPN in combination with other neurologic conditions, a significant negative correlation between NIS-W and JAMAR grip strength also exists, likely because of the LDSMPN component. 3. JAMAR grip strength may be a useful surrogate marker of global muscle strength (as measured by NIS-W) in LDSMPN, in both longitudinal clinical neuropathy assessments and as an endpoint in neuropathy clinical trials.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: Mayo Clinic Arizona Department of Neurology

Keywords: Neurological examination, Neuropathy impairment score, JAMAR grip strength, Endpoints, Clinical trials

Intraepidermal Nerve Fiber Density in Disease: A Scoping Review

Poster No:
P 250

Authors:
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Institutions:
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Introduction:
Quantifying intraepidermal nerve fiber density (IENFD) has become a critical biomarker for neuropathy diagnosis and research. The consequences of IENFD reductions include sensory dysfunction, pain, and a significant decrease in quality of life. Here, we examined publications in human and rodent models and compared the degree of IENFD loss between diseases to understand the breadth of IENFD-related complications.

Methods:
We conducted a scoping review of publications that used IENFD as a biomarker in human and non-human research. PubMed was used to identify 1,004 initial articles that were then screened to select articles that met the criteria for inclusion. Criteria were chosen to standardize publications so they could be compared rigorously and included having a control group, measuring IENFD in a distal limb, and using PGP9.5.

Results:
We analyzed 397 articles and collected information related to publication year, the condition or disease studied, and the percent IENFD loss. The analysis revealed that IENFD loss is prevalent in many diseases, and metabolic or diabetes-related diseases were the most studied condition in humans and rodents. Our analysis identified over 70 human diseases in which IENFD was affected, with the majority reporting IENFD loss at a mean of -47%. We present data describing subanalyses of IENFD loss according to disease characteristics in diabetes and chemotherapy treatments. Within animal models, we provide insight into IENFD loss in different diabetes models, chemotherapy types, and rodent species.

Conclusions:
Reduced IENFD occurs in a surprising number of human disease conditions. Abnormal IENFD contributes to important complications, including poor cutaneous vascularization, sensory dysfunction, and pain. Our analysis informs future rodent studies so they may better mirror human diseases impacted by reduced IENFD, highlights the breadth of diseases impacted by IENFD loss, and urges exploration of common mechanisms that lead to substantial IENFD loss as a complication in disease.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: 1T32DK128770-01A1 NINDS R01NS043314-17

Keywords: degeneration, axon, epidermis, neuropathy, sensory

Utility of Sural Nerve Conduction in Electrodiagnosis of Polyneuropathy in General Neurology Clinics

Poster No:
P 251

Authors:
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Introduction:
Guidelines on polyneuropathy often state that for electrodiagnostic support of the diagnosis there should be at least abnormal nerve conduction of the sural nerve. As this recommendation is based on research conducted in a specialized clinical neurophysiology department, this study aims to assess whether this can be generalized to the daily practice of general neurology clinics without a specialized clinical neurophysiology department.

Methods:
In this retrospective observational study, we collected nerve conduction studies of patients with chronic idiopathic axonal polyneuropathy (CIAP) when performed and available in both a specialized neuromuscular clinic and referring general neurology clinic. The maximum interval between these two nerve conduction studies was set at two years as previous studies have shown electrodiagnostic abnormalities in CIAP to be relatively stable. We used kappa analysis and Spearman correlation to compare sural nerve amplitude measurements.

Results:
The preliminary results suggest a moderate to strong correlation between the amplitude values measured in the specialized neuromuscular clinic and general neurology clinic. However, there is a low agreement on whether the sural nerve recording was obtainable. Low amplitudes and, in a smaller proportion, normal amplitudes, were reported as not obtainable by general neurology clinics.

Conclusions:
As data collection is ongoing, more definite results of this study will be presented at the upcoming PNS annual meeting.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: EMG, nerve conduction studies, sural nerve amplitude

Knowledge Gaps In Diagnosing Polyneuropathy: A Review Of National Guidelines

Poster No:
P 252

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Institutions:
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Introduction:
Polyneuropathy is a common neurological disease. Because polyneuropathy particularly affects middle aged and elderly people, the number of patients with polyneuropathy is expected to increase due to the aging population. This rising number of patients with polyneuropathy is an important reason to streamline the diagnostic process, also for international cooperation. However, it is unknown which blood tests and when nerve conduction studies (NCS) are necessary in diagnosing patients with polyneuropathy. Therefore, as a first step, we aim to provide an overview of recommendations made in national guidelines from different countries, asses the evidence used for these recommendations and identify the knowledge gaps.

Methods:
National guidelines were obtained using PubMed and the websites of the national neurology associations. If the guideline was not available online, we contacted neurology associations of different countries by email to obtain guidelines. Online translation tools were used if necessary. We evaluated the national guidelines and the strength of evidence for recommendations regarding the workup.

Results:
We identified six (Dutch, German, French, American, Danish and Norwegian) guidelines. Every guideline recommends extensive blood tests. NCS is generally considered as essential by every guideline. However, the evidence these recommendations are based on is graded as low.

Conclusions:
The recommendations from different national guidelines pertaining the workup in patients with polyneuropathy are comparable, but all evidence for the recommendations is graded as low. There are knowledge gaps about the necessary workup in patients with polyneuropathy. These knowledge gaps are currently addressed in the ongoing EXPRESS study in the Netherlands.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Guidelines, Workup, Diagnostic process, Polyneuropathy

Neuropathic Pain Consortium (NPC) Abstracts

P 253 - 293

Assessing Sudomotor Function, Utility in Small Fiber Neuropathy Clinics: Large UK Single-Center Cohort Experience

Poster No:
P 253

Authors:
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Introduction:
Small Fiber Neuropathy (SFN) is a prevalent, often debilitating condition, typically characterised by distal damage to small diameter neurones causing symptoms such as neuropathic pain and paraesthesia. The current EFNS diagnostic criteria require clinical assessment, skin biopsy (SBx) for intraepidermal nerve fibre density (IENFD) and thermal threshold testing (TTT). A negative nerve conduction study (NCS) is required to exclude large fibre neuropathy. Sudoscan is a point of care device that measures the Electrochemical Skin Conductance (ESC) from the palms and soles to determine the autonomic sudomotor dysfunction in SFN. Its utility in a large unselected independent cohort is not well understood. ESC is routinely assessed in our SFN clinic. We investigated whether use of the Sudoscan device alongside current investigations for SFN improves diagnostic accuracy and its utility as a SFN screening tool.

Methods:
Patients attending our SFN clinic from 2019 to 2023 were recruited. From the total cohort of 456 patients, 130 fulfilled the inclusion criteria: minimum of a Sudoscan and SBx and a negative NCS. SFN symptoms were assessed using a number of standardised questionnaires.

Results:
A detailed analysis of the sensitivity and specificity of quadruple testing to aid SFN diagnosis was undertaken including calculation of area under the curve. When comparing ESC with SBx IEFND as gold standard, sensitivity=42% and Specificity=68%. When ESC was adjusted for weight, sensitivity increased to 71% and specificity decreased to 51%. Unadjusted ESC compared with TTT: sensitivity=43%, specificity=77%. Comparison of Unadjusted ESC with TTT and SBx: sensitivity= 42%, specificity=82%. ESC and TTT compared with IEFND: sensitivity=70%, specificity=62%. TTT was compared with SBx as baseline for current guidelines; sensitivity=77%, specificity=53%.

Conclusions:
Unadjusted ESC combined with TTT has better performance in predicting IENFD, suggesting that assessment of sudomotor function alongside the current SFN investigations can improve diagnostic accuracy and can aid in prediction of diagnosis whilst awaiting IENFD results.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Neuropathic pain, Small Fiber neuropathy, SUDOSCAN, Diagnostic criteria, Skin biopsy

Gene-Wise Aggregation Analysis In Chronic Pain Reveals A Mutational Burden In TRPA1

Poster No:
P 254

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Institutions:
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Introduction:
The missing heritability for adult-onset chronic pain is unlikely to be resolved by single-variant analysis approach and may be hidden within rare variants that have low to moderate effect on disease risk. To identify new genetic risk factors, we collapsed sets of qualifying rare variants within genes through gene-wise aggregation analyses and compared the allele frequency between patients with pain and healthy individuals.

Methods:
We performed next-generation sequencing of 107 genes involved in pain signaling or modulation, collapsing rare variants (GnomAD frequency<0.01) through gene-wise aggregation analysis. The Optimal Unified Sequence Kernel Association Test was applied to 169 painful neuropathy patients, 223 nociplastic pain patients (82 chronic widespread pain and 141 fibromyalgia), and 216 healthy controls. Findings were validated in two independent cohorts of 140 chronic pain patients (90 painful neuropathy and 50 chronic widespread pain) and 34 painless neuropathy patients. The effect of aminoacidic changes were modeled in silico according to physicochemical features.

Results:
TRPA1 was significant enriched of rare variants discriminating chronic pain patients from healthy controls after Bonferroni correction (p-value=6.7x10-4, rho=1) with a 4.8-fold higher risk based on the simple burden test (p=0.0015, OR=4.8). Variants were mainly clustered in the N-terminal domain containing the ankyrin repeats, essential for channel regulation. Irrespective of the clinical diagnosis, more than one third of patients complained of episodic itch and cold-triggered pain.

Conclusions:
Our study has widened the spectrum of channelopathy-related chronic pain disorders and contributed to bridging the gap between patients' phenotype and molecular alterations which may be important in the design of new targeted clinical trials in painful neuropathy.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: This work was supported by funding from the Molecule-to-Man Pain Network, European Commission Multi-Center Collaborative Projects through the European Union’s Horizon 2020 research and innovation program under grant agreement no. 721841, the PROPANE study

Keywords: neuropathic pain, nociplastic pain, gene burden, TRPA1, NGS

High Dimensional Immune Cell Profiling of Peripheral Blood in Lumbosacral Radiculopathy: A Pilot Study

Poster No:
P 255

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Introduction:
Preclinical models demonstrate the potential role of peripheral immune cells in the development and resolution of neuropathic pain after nerve injury. However, a detailed understanding of the cellular immune response to peripheral nerve injury in humans is lacking. Here we sought to profile the variation in peripheral blood mononuclear cells (PBMCs) in the context of painful lumbosacral radiculopathy.

Methods:
PBMCs and serum from 20 donors immediately prior to lumbosacral decompression/discectomy, as well as 10 sex-matched healthy controls, were isolated from whole blood and cryopreserved. We quantified the innate and adaptive immune cell populations in PBMCs by full-spectrum flow cytometry using a custom-designed 23-colour panel, with a focus on markers of cytotoxic immunity. Serum levels of inflammatory cytokines were analysed by U-plex assay.

Results:
We observed a significant increase in the proportion of CD4+ helper T (Th) cells in the radiculopathy group versus controls, among which there was a non-significant trend for greater regulatory T (Treg) cells. Conversely, we observed a decrease in the proportion of monocytes, while there were no significant differences in total NK, CD8+ T, B cell and dendritic cell populations between groups. T-distributed Stochastic Neighborhood Embedding (t-SNE) analysis of cell subsets revealed a significant decrease in CD127+CD57- γδ T cells in the radiculopathy cohort. NK cells showed elevated levels of the cytotoxicity-related protein perforin, compared to healthy donors. We also observed an increase in the granzyme B-producing CD8+ NKT cells, and decrease in CD127-CD57+ γδT cells producing perforin and granzyme B. Serum levels of interferon gamma (IFN-γ), interleukin 4 (IL-4) and IL-12p70 showed a decreasing trend in the patient cohort.

Conclusions:
This study serves as a foundation to the further immune cell profiling in peripheral nerve injury and neuropathic pain. Future work will examine the dynamic changes in cell populations post-surgery and their relationship to pain outcomes.

References:
Yes

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References 2:
Royds, J and McCrory, C. (2018) Neuroimmunity and chronic pain. BJA Educ 18 (12), 377-383.

References 3:

References 4:

Grant Support: This work is supported by a UKRI Future Leaders Fellowship award (MR/V02552X/1) and a Human Immune Discovery Initiative award from the NIHR Oxford Biomedical Research Centre.

Keywords: immune cell, cytokine, cytotoxic immunity, lumbosacral radiculopathy, neuropathic pain

Peripheral Nerve Reinnervation of a Combined Dermal and Muscle Graft Construct Prevents Neuropathic Pain After Transection Injury

Poster No:
P 256

Authors:
Widya Adidharma[1], Sara Huang[1], Ritvik Jillala[1], Maria Santana-Rivera[1], Keith Kozma[1], Alex Vaskov[1], Paul Cederna[1], Stephen Kemp[1]

Institutions:
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Introduction:
Symptomatic neuromas can form after peripheral nerve transection, which cause debilitating pain and affect one's quality of life. We developed the Composite Regenerative Peripheral Nerve Interface (C-RPNI) for prevention of neuroma formation. The C-RPNI involves prophylactically implanting a transected mixed motor and sensory peripheral nerve into a biologic construct composed of both a de-epithelialized dermal graft and free muscle graft. We hypothesized that the C-RPNI leverages the inherent preferential reinnervation properties of mixed peripheral nerves to promote cutaneous afferent reinnervation of the dermal sensory end organs and motor efferent reinnervation of muscle fibers in the construct, thus preventing neuroma formation.

Methods:
Twelve male rats were randomly assigned to one of the following groups (n=6/group): (1) C-RPNI, and; (2) neuroma. For the neuroma group, the left common peroneal nerve was transected at the distal thigh level, and the proximal nerve segment was relocated directly beneath the skin. In the C-RPNI group, the proximal transected segment was implanted between a dermal and muscle graft, and the C-RPNI was placed under the skin. Bi-weekly behavior tests were performed for 3 months post-operatively. Neuroma pain was assessed by trials of 5 gentle taps over the neuroma/construct using a Von-Frey filament (similar to Tinel's test). Cold allodynia was assessed using the standard acetone drop test. At study endpoint, neuroma bulbs and C-RPNIs were harvested, and immunohistochemistry of nerve fibers and end organ targets was performed.

Results:
At 3 months postoperatively, the C-RPNI is viable and revascularized. There is reinnervation of end organ targets in both the muscle and dermal components of the C-RPNI. Animals in the C-RPNI group demonstrated less neuropathic pain when compared to the neuroma group in the behavioral tests.

Conclusions:
Regenerating mixed peripheral nerves can reinnervate dermal and muscle grafts after transection injury. Treatment with prophylactic C-RPNI can mitigate neuropathic pain.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: nerve regeneration, neuroma, neuropathic pain, neuroma treatment, peripheral nerve injury

Functional Reinnervation of a Peripheral Nerve Interface After Nerve Transection Can Facilitate Sensory Feedback and Prevent Neuroma Formation

Poster No:
P 257

Authors:
Widya Adidharma[1], Maria Santana-Rivera[1], Ritvik Jillala[1], Keith Kozma[1], Paul Cederna[1], Stephen Kemp[1]

Institutions:
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Introduction:
After amputation, sensory nerve injury can cause sensory loss and peripheral neuropathy. This is in part due to the lack of cutaneous end-organ targets that can be reinnervated for facilitating sensory feedback and preventing neuroma formation. Advanced prosthetics have sensors that can detect sensory stimuli. However, attempts in re-establishing sensory feedback lead to unnatural, non-specific, and/or painful sensations due to shortcomings in available patient-prosthetic nerve interfaces. We hypothesized that physiologic reinnervation of a dermal graft wrapped around a transected sensory peripheral nerve (termed Dermal Sensory Regenerative Peripheral Nerve Interface or DS-RPNI) can serve a dual purpose: preventing neuroma formation and facilitating afferent sensory signaling as a biologic patient-prosthetic interface.

Methods:
Fifteen male rats were randomly assigned to one of the following groups (n=5/group): (1) DS-RPNI, (2) acellular dermal matrix (ADM; lacks sensory end-organs), and (3) naive control (sural-innervated lateral hindpaw). The sural nerve was transected at the distal thigh level in DS-RPNI and ADM groups, and the proximal nerve segment was implanted into dermal graft or ADM, respectively. After 3 months, in situ sural compound sensory nerve action potentials were recorded during application of sensory stimuli to the constructs or control lateral hindpaw. The following sensations were tested: fine touch, vibration, noxious heat, and noxious cold.

Results:
Immunohistochemistry revealed reinnervation of sensory corpuscles and regeneration of free nerve endings in the DS-RPNI, which was not seen in ADM constructs. There was no neuroma formation in the DS-RPNI group. Compared to control, stimulation of DS-RPNI generated similar signals for vibration and greater signals for noxious temperatures. Compared to ADM, DS-RPNI generated higher amplitude signals for both tactile and noxious sensations.

Conclusions:
DS-RPNI prevents neuroma formation in sensory nerves. Functional reinnervation of this novel biologic interface facilitates multimodal sensory signaling and may revolutionize the frontier of prosthetic sensory feedback and neuroma management.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: nerve regeneration, neuroma, neuropathic pain, neuroma treatment, peripheral nerve injury

Evaluation of Neuropathic pain using analysis of the patterns of bone Scintigraphy

Poster No:
P 258

Authors:
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Institutions:
[1]N/A, seoul, Korea, Republic of, [2]Kanmgnam Sacred Heart Hospital, Seoul, Korea, Republic of

Introduction:
Neuropathic pain is often described as a burning, shooting, pricking, pins and needles, squeezing, or freezing pain. Neuropathic pain patients complain more often of cold than warm allodynia, although both signs are found on examination. Cold allodynia is particularly common in central pain, small fiber neuropathy. Small fibre neuropathy (SFN) is a sensory, typically painful, disease of thin myelinated and unmyelinated nerve fibers. The diagnostic criteria for small fibre neuropathy are not established yet. Proposed diagnostic criteria for small fiber neuropathy require a combination of clinical signs (pinprick and thermal sensory loss, allodynia, hyperalgesia) and abnormal intraepidermal nerve fibre density(IENFD) or quantitative sensory testing . Skin biopsy is an invasive procedure accompanied by pain, it has some clinical limitations. Alternative tests for small fiber function are corneal confocal microscopy, SSR(Sympathetic skin response) and QST(quantitative sensory testing). In this study, we evaluated the patients with neuropathic pain mainly presenting cold allodynia using three phase bone scan.

Methods:
Three phase bone scan and routine nerve conduction study data were collected from 16 patients with neuropathic pain, especially cold sensation, paresthesia and allodynia.

Results:
Ten of the 16 patients were female. 7 patients showed sensorimotor polyneuropathy on routine nerve conduction study, 3 of them had diabetes. Three phase bone scan was normal in 6 patients. The uptake ratio of three phase bone scan were decreased and the blood pooling time was showed delayed tendency in neuropathic pain patients with cold sensation and allodynia.

Conclusions:
Three phase bone scan could be used as assistant tool to evaluate neuropathic pain with routine NCS .

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: No

Keywords: neuropathic pain

Mechanism of β-arrestin-biased Agonism at M1 Muscarinic Receptor of Adult Sensory Neurons: Role in Neuritogenesis

Poster No:
P 259

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Introduction:
We recently showed that application of selective (pirenzepine (PZ)) or specific (muscarinic toxin 7 (MT7)) antagonists of muscarinic acetylcholine type 1 receptor (M1R) reverse sensory nerve degeneration in different rodent models of peripheral neuropathy. In vitro studies have confirmed that β-arrestin played a role in mediating these effects. To understand the mechanism of action of PZ and MT7, we investigated whether these drugs possess β-arrestin-biased agonism at M1R of sensory neurons to drive neurite outgrowth.

Methods:
Human embryonic kidney (HEK) 293 cells and cultured adult rat dorsal root ganglia (DRG) sensory neurons were used. The signaling and trafficking properties of muscarinic drugs were characterized using inositol-phosphate one (IP1) measurement, Nano bioluminescence resonance energy transfer (NanoBRET), and luminescence-based M1R internalization assay. Phospho-specific immunoblotting for serine and threonine residues was performed on M1R purified from HEK293 cells overexpressing Halo-tagged M1R. Role of Gαq-protein and β-arrestins in PZ/MT7-induced ERK activation was investigated using a specific Gαq inhibitor and β-Arrestin KO HEK293 cells, respectively.

Results:
M1R agonists and antagonists induced Halo-tagged β-arrestin2 recruitment to M1R-Nluc in a dose-dependent manner. Unlike MT7 and PZ, muscarine increased IP1 levels, while both PZ and MT7 dose-dependently inhibited muscarine-induced IP1 generation. Also, MT7 and PZ increased ERK phosphorylation in both M1R-expressing HEK293 and DRG neurons in a time-dependent manner. This drug-induced activation of ERK was mechanistically linked to elevated neurite outgrowth in DRG neurons. These results suggest PZ/MT7 possess β-arrestin-biased agonism. β-arrestins (and not Gαq protein) were necessary for PZ/MT7-induced ERK phosphorylation. Further, both PZ/MT7 impacted serine/threonine phosphorylation status of M1R. Surprisingly, PZ/MT7 not only did not induce M1R internalization but increased surface expression of the receptor.

Conclusions:
Overall, this study provides molecular evidence to support a role for selective/specific muscarinic receptor antagonists acting as biased agonists at the M1R to drive neurite outgrowth and prevent/reverse nerve degeneration in peripheral neuropathy.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Biased agonism, Muscarinic M1 Receptor, Sensory neurons, Beta-arrestin signaling

Clinical Trials Network Develops Platform Protocol to Assess Non-addictive Therapeutics for Painful Diabetic Peripheral Neuropathy.

Poster No:
P 260

Authors:
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Introduction:
As part of the NIH HEAL (Helping to End Addiction Long-term) Initiative, the National Institute of Neurological Disorders and Stroke established the Early Phase Pain Investigation Clinical Network (EPPIC-Net) to accelerate clinical trials of non-addictive pharmacologic/non-pharmacologic therapeutics ('assets') for pain conditions of high unmet need. The network provides infrastructure for conducting high quality multi-site clinical trials and has the capacity to simultaneously run several multi-site trials.

Methods:
Painful diabetic peripheral neuropathy (PDPN) is a common pain condition with high unmet therapeutic need. Here we introduce EPPIC-Net's innovative platform protocol, designed for Phase 2 clinical trials of assets targeting PDPN. While platform trials have been used successfully in other fields (e.g., cancer therapeutics), they are novel for pain. EPPIC-Net's PDPN platform protocol provides a common overarching structure that includes both required and optional modules. The required modules provide efficiency and consistency across assets. The optional modules allow asset-specific elements to be incorporated as trials of future PDPN assets are added.

Results:
EPPIC-Net's PDPN protocol utilizes overarching eligibility criteria for randomization to an asset and asset-specific requirements. Efficiency is achieved through common screening procedures, common data elements and case report forms, and a potential to utilize common control groups (placebo/active comparator). The platform approach also allows for the study of biomarkers across multiple assets. The primary efficacy endpoint is the change in weekly average of the daily NRS (0-10 pain numerical rating score). To date, two assets have been approved for funding under EPPIC-Net's PDPN platform protocol. The trial of one of the PDPN assets is currently open to enrollment.

Conclusions:
EPPIC-Net continues to accept new applications for non-addictive pain therapeutics from industry, academia, and not-for-profit organizations, located worldwide. Applications are accepted and reviewed on a rolling basis.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Painful diabetic peripheral neuropathy , Platfrom protocol, Clinical Trials Network

Signs Of Peripheral Neuropathy, Physical Function Tests And Autonomic Dysfunction In A Gerontological Population Study

Poster No:
P 261

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Introduction:
As demography changes to increasing life expectancies, peripheral neuropathy can be expected to become more common. A few reports present a prevalence of peripheral neuropathy of up to 7% in aging populations. The aim of this population study was to investigate the extent of signs of peripheral neuropathy in 2996 Swedish community-dwelling adults ages 60–97 years old, and its associations to physical and autonomic nerve system function.

Methods:
Signs of peripheral neuropathy were graded on the Utah Early Neuropathy Scale (UENS). Physical tests, pain, falls, fear of falling, and use of walking aids, and tests and symptoms of autonomic dysfunction were studied in four quantiles per UENS score (Q1–Q4), stratified by gender.

Results:
Participants in Q4 in both genders had significantly high odds ratios (OR) of failing One leg balance test (Male OR 2.6 [CI 95%: 1.7–4.1]; Female OR 1.9 [1.1–3.2]) and Balance pad test (Male OR 4.6 [3.2–6.7]; Female OR 1.8 [1.3–2.6]), and significantly worse Estimated Marginal Means on Timed Up and Go (Q4–Q1: Male 10.8–9.6 s; Female 11.7–10.2 s), 15 m walking test (Q4–Q1: Male 11.1–9.9 s; Female 11.2–10.4 s) and Step test (Q4–Q1: Male 15.2–17.0 steps; Female 14.5–15.8 steps). Participants in Q4 also had significantly higher odds of using walking aids, lower limb pain, falls or fear of falling, and urinary incontinence. For males the odds ratios for orthostatic intolerance, fecal incontinence and constipation were also significantly increased.

Conclusions:
In 20–25% of an unselected population of older adults, early signs of peripheral neuropathy affected tests of mobility, gait, and balance, and were also associated with markers of autonomic dysfunction.

References:
Yes

References 1:
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References 2:
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References 4:
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Grant Support: The Swedish Ministry of Health and Social Affairs, the Skåne Regional Council, and the Swedish Medical Research Council no. 2017-01613; 2017-00639.

Keywords: Utah Early Neuropathy Scale, Balance, Gait, Epidemiology, Older adults

Ultrasonography of the vagus nerve in small fiber neuropathy

Poster No:
P 262

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Institutions:
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Introduction:
Small fiber neuropathy (SFN) is a disorder of thin myelinated A-delta and unmyelinated C nerve fibers. Patients experience neuropathic pain, most often in a length-dependent distribution. Dysautonomia can be present as well. The vagus nerve (VN) plays in important role in regulation of autonomic functions and consist mainly out of unmyelinated small nerve fibers. In patients with diabetic neuropathy and Parkinson's disease – in which autonomic dysfunction can be experienced – it has been shown that the cross sectional area (CSA) of the VN is reduced. We hypothesize that the VN is atrophied – and thus has a smaller CSA – in SFN patients in comparison with healthy subjects. Also, a negative association between the CSA and the appearance of autonomic complaints is expected.

Methods:
In 56 SFN patients and 53 age- and sex-matched healthy controls the CSA of both VN was measured using ultrasound. Patients and controls were categorized per decade with an equal distribution between males and females. Autonomic complaints were measured using the SFN Symptom Inventory Questionnaire (SFN-SIQ) and Scales for Outcomes in Parkinson's Disease-Autonomic questionnaire (SCOPA-AUT). Pain was measured using the neuropathic pain scale (NPS).

Results:
The results of this study will be presented at the congress.

Conclusions:
Depending on the results, we will conclude whether ultrasound of the vagus nerve is a reliable additional diagnostic test in the diagnosis of small fiber neuropathy.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: small fiber neuropathy, ultrasonography, vagus nerve, dysautonomia

Neuropathic Pain In Patients With Anti-Caspr2 Autoantibodies

Poster No:
P 263

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Introduction:
Autoantibodies against caspr2, a protein of the voltage-gated potassium channel complex, are known to induce autoimmune encephalitis and neuromyotonia. Neuropathic pain is another characteristic symptom in some but not all patients with anti-caspr2 autoantibodies.

Methods:
Here, we aimed to determine the frequency of anti-caspr2 autoantibodies in a cohort of patients with painful small and/or large fiber neuropathy (n=71) and to characterize neuropathic pain in a large cohort of patients with anti-caspr2 autoantibodies (n=100) recruited by the German Network for Research on Autoimmune Encephalitis (GENERATE).

Results:
Seventy-one patients with painful neuropathy of unknown cause were screened for autoantibodies against caspr2. Low titers were detected in two patients but were not persistent and therefore not considered relevant. All other patients were negative, indicating that anti-caspr2 autoantibodies seem to be a very rare cause of painful neuropathy if no other symptoms are associated. In the cohort of anti-caspr2-positive patients, the disease was associated with pain in 33% of patients, pain being the major symptom in 60% of the patients who experienced pain. Pain phenotypes comprised distal-symmetric neuropathic pain, resembling small fiber neuropathy (SFN-like pain) (43% of all patients with pain) as well as back pain radiating to the legs/arms (20%) and chronic widespread pain/myalgia (37%). Pain was rated as severe by 71.4 % of the patients, as moderate by 23.8% and as mild by 4.8%. In only 42% of the patients, SFN-like pain responded to immune therapy whereas treatment response was reported in 63% of patients with other pain phenotypes.

Conclusions:
Our data show that pain is a relevant symptom in a subgroup of patients with anti-caspr2-associated disease, comprises different pain phenotypes and is mostly considered as severe and disabling.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: Deutsche Forschungsgemeinschaft, KFO 5001 Teilprojekt P03

Keywords: autoantibody, caspr2, pain, small fiber, neuropathy

Neuroprotective And Neuroregenerative Effect Of A Novel TSPO Ligand In The Peripheral Nervous System

Poster No:
P 264

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Introduction:
Although adult peripheral nerves retain the ability to regenerate, functional recovery is often disappointing in cases of traumatic injury. This is often associated with the development of chronic neuropathic pain. The 18 kDa translocator protein (TSPO) and voltage-gated Kv7.2/3 potassium channels are two promising targets to promote peripheral nerve regeneration and functional recovery, thus preventing chronification of neuropathic pain. Recently, a new compound targeting both TSPO and Kv7.2/3, the GRT-X (N-[(3-fluorophenyl)-methyl]-1-(2-methoxyethyl)-4-methyl-2-oxo-(7-trifluoromethyl)-1H-quinoline-3-caboxylic acid amide), has been developed and proved to offer a promising preclinical treatment for chronification of acute pain. In this study, we assessed the role of GRT-X in promoting axonal growth.

Methods:
This proof of concept was performed on cultures of embryonic (E13.5) dorsal root ganglia (DRG) from C57BL/6JRj mice. DRG explants were extracted, treated, and divided into groups: GRT-X, XBD173 (TSPO agonist), ICA27243 (Kv7.2/3 agonist), XE991 (Kv7.2/3 antagonist), ethanol (vehicle), and non-treated DRGs (NT).

Results:
The immunostaining with the heavy neurofilament (NFH) antibody at 96h followed by the quantification of neurites lengths, show an increase in axonal growth after GRT-X treatment compared to the other groups. Furthermore, the positive effect of GRT-X on axonal growth was higher than the other groups at different time points (Day4, and Day8) and at different doses (1 or 2 treatments). Also, RT-qPCR studies showed greater increases in the expression levels of genes involved in development, myelination, and axonal growth 96h after GRT-X treatment compared to the other groups. Additionally, no significant differences in neurites lengths were observed between the different groups in cultivated TSPO-knockout DRG explants.

Conclusions:
These data indicate that the dual activation of TSPO and Kv7.2/3 by GRT-X is crucial to promote axonal growth by lengthening the neurites and increasing the expression levels of different genes involved in development, myelination, and axonal growth, thus making GRT-X a promising candidate for post-traumatic axonal regeneration.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: TSPO , Kv7.2/3, Embyonic dorsal root ganglia, Axonal growth, Traumatic injury

In vitro Characterization Of Different Decellularization Protocols for Peripheral Nerve Grafts Preparation.

Poster No:
P 265

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Introduction:
In critical nerve gaps, where tensionless repair is unapplicable, a nerve graft or conduit are needed to connect the two nerve stumps. Decellularized nerve allografts are a promising tissue engineering strategy. Their superiority over nerve conduits is owed to the availability of natural well-conserved extracellular matrix (ECM) components that has proven to play an important role in supporting axonal guiding and peripheral nerve regeneration. The known decellularization techniques nowadays are time and effort consuming. In the present work performed on rat sciatic nerves, we investigated a novel nerve decellularization protocol able to combine an effective decellularization in short time with a good ECM preservation.

Methods:
Two different decellularization protocols were tested. The first protocol - proven to be efficient for decellularizing tendons (DN-P1), using 1% tri(n-butyl) phosphate (TBP), 3% peracetic acid (PAA) (Lovati et al., 2016) - was compared with a decellularization protocol specifically developed for nerves (DN-P2), using 125mM SB-10, 0.2% TritonX-100, 0.25% SDS, and sonification cycles (Boriani et al.; 2017). The outcomes of both decellularization protocols were assessed by a series of in vitro evaluations, including qualitative and quantitative histological and immunohistochemical analyses, DNA quantification, SEM and TEM ultrastructural analyses, mechanical testing, and viability assay.

Results:
Both decellularization protocols had led to an overall well-preserved nerve structure; DNA quantification showed that DNA content was significantly decreased, but not completely removed. Both protocols had less cellular component, but complete removal was not achieved; an adequate amount of ECM component is still conserved in both protocols. DN-P1 has better biomechanical properties, superior biocompatibility and ultrastructural properties compared to DN-P2.

Conclusions:
DN-P1 greatly demonstrated superior results compared to DN-P2 in terms of ultrastructural analysis and biocompatibility. Decellularized nerve allografts prepared following DN-P1 protocol are promising for long gap repair in vivo.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Nerve Allograft, Decellularization, Nerve Repair

Proof-of-concept Study of Topical Amitriptyline for Erythromelalgia

Poster No:
P 266

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Introduction:
Erythromelalgia (EM) is a rare disease, with an estimated 15,000 sufferers in the US and Europe, involving episodes of pain and erythema, usually in the extremities. There are no approved therapies and extremely few randomized interventional trials published. Most patients take multimodal pharmacotherapy, including standard analgesics, antidepressants, gabapentinoids, antihistamines, etc, but with limited effectiveness. Many patients resort to potentially damaging measures for symptomatic relief, such as prolonged immersion of feet in ice water. The tricyclic antidepressant amitriptyline (AMT) is used in various neuropathic pain indications. Its mechanism of action on the peripheral nervous system has recently been elucidated and is different from its well-established central nervous system action. AMT was found to be a potent inhibitor of sodium channels (Nav), especially Nav 1.7, 1.8 and 1.9, inhibiting the firing activity of A and C fibres, leading to alleviation of neuropathic pain. Dysfunction of these sodium channels is known to be involved in EM-associated neuropathic pain. A proprietary hydrogel, ATX01, containing 15% w/w AMT, has previously been shown in healthy volunteers to deliver high concentrations of AMT locally with low systemic penetration and few side effects. This may therefore have efficacy and safety advantages over oral AMT.

Methods:
We are therefore conducting a randomized, double-blind, placebo-controlled, crossover trial to investigate the efficacy and safety of ATX01 in EM patients. Fourteen male and female adult EM patients will be enrolled at two centres, one US and one German. Following a three-week baseline assessment, patients will receive three-week courses of twice-daily applications of ATX01 and matching placebo, in random order, separated by a three-week wash-out period.

Results:
The primary endpoint is mean pain intensity per episode, assessed for the final week of each treatment period using an 11-point numerical pain rating scale.

Conclusions:
We aim to have data by the end of 2023.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Erythromelalgia, Neuropathic pain, Amitriptyline, Voltage-gated sodium channel, Topical

Translational Model of Nerve Injury-on-Chip

Poster No:
P 267

Authors:
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Introduction:
Day to day life can lead to traffic accidents, injuries at the workplace, incidents at home or during hobbies. Consequences can be devastating and include complete loss of motor function or chronic neuropathic pain due to nerve damage. Peripheral nerves are made of motor and sensory nerves, two very distinct types of neurons that are linked but each have their specific function. Organs-on-chip (OoC) offer the advantage to isolate neuron somas from their axons, thus reproducing the human anatomical architecture and enabling injury or treatment paradigms aligned with real life situations.

Methods:
To tease apart each cell type and allow their study separately, we adapted the culture of motorneurons and sensory neurons onto our OoC platform. To bridge the gap between in vivo models and first-in-human studies, as well as increase relevance, we developed our models using hiPSC-derived neurons. As a mirror of current in vivo models, such as nerve crush injury or nerve ligation that aim to mimic human nerve trauma, we created a repeatable and standardized injury, by cutting, motor or sensory axons only using a short, targeted detergent application. The specific shape of NETRI's DuaLink Delta Ultra chips and our live staining protocol, combined with the high-throughput format of the NeoBento allow to easily monitor the neurite outgrowth dynamics during the whole period of drug application.

Results:
We validated our models by comparing axonal regeneration following treatment with neurotrophic molecules or drugs inhibiting neurite outgrowth.

Conclusions:
To summarize, we offer pharmaceutical companies and researchers a new translational model of traumatic nerve injury to study efficacy and mode of action of novel therapeutic modalities.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Organs-on-chip, Pain, Nerve Injury, hiPSC, Translational

Experienced Sampling Method In Small Fiber Neuropathy: Influence Of Psychosocial Factors On Pain And Disability

Poster No:
P 268

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Introduction:
Small fiber neuropathy (SFN) is a chronic condition in which the small nerve fibers are affected, resulting in neuropathic pain and autonomic dysfunction. Current treatments are mostly based on symptomatic pain relief, but are often insufficient with a lot of side effects. In chronic pain conditions, pain intensity and pain-related disability seem to be caused and influenced by several bio-psychosocial factors, such as catastrophizing, anxiety, fear, and depression, and are associated with a decreased quality of life. It is important to understand how psychosocial factors fluctuate over time and influence pain intensity and pain-related disability, to be able to optimize personalized treatment. Measuring biopsychosocial factors is possible with several questionnaires, however, they are not able to detect changes and fluctuations. Experienced sampling method (ESM) does contain these features, allowing a more profound understanding of disease-related changes. The aim of this study is to gain insight in the influence of psychosocial factors on pain intensity and pain-related disability by using ESM.

Methods:
The study is a prospective observational study with repeated measurements. Participants with idiopathic SFN, older than 18 years, with an indication for rehabilitation treatment were included. The PsyMate application (smarteHealth GmbH, Luxembourg) for smartphones has been used to gain information about daily functioning and pain. A scheme of 10 signals a day for seven consecutive days has been programmed. A baseline questionnaire had to be completed, including Pain Catastrophizing Scale, Hospital Anxiety and Depression Scale, SF-12, and SFN-specific questionnaires: SFN-specific Rasch built Overall Disability Scale and SFN-specific Symptom Inventory Questionnaire.

Results:
The ESM-data of 21 participants has been analyzed with multilevel analysis with a backward stepwise approach.

Conclusions:
The results will be presented.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Small fiber neuropathy, Pain-related disability, Psychosocial Factors, Mobile Application, Quality of life

Transthyretin Familial Amyloid Polyneuropathy (TTR-FAP): Demyelinating electroneuromyographic findings in newly diagnosed patients

Poster No:
P 269

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Introduction:
The classic clinical manifestation of TTR-FAP is progressive length-dependent polyneuropathy, with expressive involvement of small fibers. Although the typical neurophysiological finding of PAF-TTR is axonal sensory-motor polyneuropathy, it is common to observe heterogeneous patterns of presentation in electroneuromyography. This variability may delay diagnosis and impair the initiation of treatment for these patients. In these cases, knowledge about the neurophysiological findings of FAP can be used as an auxiliary tool in the differential diagnosis.

Methods:
The study was performed in two neuromuscular diseases reference centers in Rio de Janeiro, Brazil. We selected 18 patients diagnosed with TTR-FAP confirmed by genetic study and/or nerve biopsy and who underwent electroneuromyography at the time of diagnosis. The neurophysiological data obtained were classified and correlated with clinical and functional findings.

Results:
The most common neurophysiological pattern found at the time of diagnosis of these patients was axonal polyneuropathy, which was found in eleven patients (61.1%). Predominance of axonal sensory-motor polyneuropathy corroborates data found in literature. Four patients (22.2%) showed signs of demyelination in electroneuromyography. All had severe associated axonal involvement. All of them met the European Federation of Neurological Societies/Peripheral Nerve Society criteria for definitive chronic inflammatory demyelinating polyradiculoneuropathy.

Conclusions:
Axonal compromise was predominant in the different mutations evaluated in the study, however demyelinization findings can occur as a primary lesion. Demyelination was a remarkable finding and, although atypical, should not rule out this difficult diagnosis.

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Yes

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Grant Support:

Keywords: Amyloidosis, Peripheral neuropathy, Electroneuromyography, Neurophysiology, Transthyretin

Non-Systemic Peripheral Nervous System Vasculitis Cases In a Specialized Center In Brazil

Poster No:
P 270

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Introduction:
Introduction – Non-systemic peripheral nervous system vasculitis is an extremely rare form of single-organ vasculitis. It usually has a heterogenous presentation that makes it challenging to make an early diagnosis, resulting in chronic pain and disabilities. We hope that the present study expands the knowledge of the disease, leading to an earlier diagnosis and better treatments in the future.

Methods:
Methods – We have selected patients that have received the diagnosis of non-systemic peripheral nervous system vasculitis during the study's data collection period. We have included patients with clinical examinations, electroneuromyography (EMG), and biopsy findings supporting the diagnosis, according to the Peripheral Nervous System Society Guidelines. We have analyzed the patients regarding these criteria.

Results:
Results – We have identified five patients that met the criteria for non-systemic peripheral nervous system vasculitis. All of them presented with pain as an early complaint. Four of them had a loss of sensation in the legs. One of them initially presented with cranial nerve palsy. All patients had EMG findings revealing an asymmetrical axonal neuropathy. 2 of them developed the condition acutely, and 3 of them had chronic progressive forms. All of them reported improvement with immunosuppressive treatment, although chronic pain and weakness were common residual findings.

Conclusions:
Conclusions – Non-systemic peripheral nerve vasculitis is an extremely rare condition of difficult diagnosis due to heterogenicity in presentation and the need for biopsy in the diagnostic algorithm. The patients usually have delayed diagnosis and treatment due to this. Immunussupresive treatment is effective in slowing progression and reducing pain and disability. This diagnosis should be considered in any patient with asymmetrical axonal neuropathy without other apparent causes.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Non-systemic Peripheral Nervous System Vasculitis, Vasculitis, Neuropathic pain

Quantifying ulnar nerve tension around the elbow using shear wave elastography

Poster No:
P 271

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Introduction:
Shear wave elastography (SWE) is one of the non-invasive methods for evaluating tissue stiffness using ultrasound. Recently, many studies have reported the application of SWE on musculoskeletal systems such as muscles, tendons, ligaments, and nerves. In one study, patients with cubital tunnel syndrome showed greater stiffness of the ulnar nerve with higher SWE values. Also, there have been studies on estimating ulnar nerve elasticity using SWE in patients who have undergone ulnar nerve decompression surgery. However, the relationship between the SWE values and the actually measured tension of the ulnar nerve around the elbow has not yet been studied yet. Therefore, in this pilot study, we aimed to explore the relationship between the mechanical extensibility of the ulnar nerve around the elbow with the SWE values.

Methods:
Total 11 fresh cadavers with 22 elbows were used in the study. SWE of the ulnar nerve was evaluated around the elbow in the cross-sectional view with 3 different elbow positions (full extension, elbow flexion 90°, and full flexion). The change in the elasticity of the ulnar nerve was simulated using a pulley system using 7 weights (0g, 20g, 50g, 100g, 200g, 500g, 1000g) with the ulnar nerve exposed by dissection on the palmar side of the wrists. SWE of the ulnar nerve was then measured in each weight in the longitudinal view.

Results:
Ulnar nerve tension was the lowest with the elbow fully extended, and SWE gradually increased with elbow flexion. Moreover, SWE of the ulnar nerve showed a positive relationship between tensile load (g) in longitudinally acquired shear wave elastography (kPa) (ρ= 1.000, p-value <0.01).

Conclusions:
SWE of the ulnar nerve around the elbow increased as the tension of the ulnar nerve increased. SWE may be utilized as a useful tool to evaluate the ulnar nerve tension around the elbow.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: ulnar nerve, shear wave elastography, ultrasound, cadavers, elbow

The efficacy and safety of 5% Lidocaine patch applied to the ileoinguinal nerve dermatome area for postoperative pain in unilateral inguinal herniorrh

Poster No:
P 272

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Introduction:
The incidence of postoperative pain is 25-30% after day-surgery. Open inguinal herniorrhaphy is one of the common surgeries performed by day-surgery that the surgical site of acute postoperative pain tends to chronic pain. We investigated effect of lidocaine patch on acute postoperative pain undergoing unilateral inguinal herniorrhaphy by day-surgery.

Methods:
This is a single-center, prospective, double-blind, randomized, controlled phase II clinical trial. Thirty-two patients were randomly allocated to placebo and lidocaine patch groups. The patients were attached patch near each participant's surgical wound at the end of surgery. We checked visual analogue scale (VAS) pain score divided three cases(resting/moving/coughing) in PACU, day-surgery unit and clinic after discharge. The primary outcome was VAS at the time of discharge from the day surgery unit. The secondary outcomes were analgesic requirement and complication of lidocaine in PACU, day-surgery unit and clinic after discharge.

Results:
There were not significant decreased VAS (resting/moving/coughing) in lidocaine patch group than placebo patch group at discharge (1.94 ± 1.06 vs 2.38 ± 1.46; p=0.34 / 3 ± 1.27 vs 3.56 ± 1.63; p=0.29 / 3 ± 1.67 vs 4.63 ± 2.73 p=0.05). In addition, there was not significant less requirement analgesic (Fentanyl) in lidocaine patch group than placebo patch group at discharge (9.69 ± 20.04 vs 21.88 ± 25.62; p=0.14). However, another variable in lidocaine patch group tends to less pain than placebo patch group.

Conclusions:
The lidocaine patch is may effective on postoperative acute pain undergoing unilateral open herniorrhaphy. As a result of this study, more sample sizes will be investigated in phase III studies.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Lidocaine patch, postoperative pain, unilateral inguinal herniorrhaphy

Diffuse large B cell lymphoma presented as unilateral trigeminal neuralgia

Poster No:
P 274

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Introduction:
Trigeminal neuralgia is a disease that can occur suddenly and become severe, chronic facial pain, and evaluation of the etiology and proper treatment are important. The causes vary, which can occur in connection with disease such as multiple sclerosis, diabetes mellitus and vascular disease. However, in many cases, it is caused by direct injury to the trigeminal nerve in posterior cranial fossa, such as odontogenic inflammation, damaged by dental procedure, root entry zone of arteriovenous malformation, aneurysm, vestibular schwannomas, malignant tumor, arachnoiditis and others. We report a case that the first impression was direct trigeminal nerve injury caused by odontogenic inflammation or after dental procedure, but the final diagnosis was malignant tumor, Diffuse large B-cell lymphoma (DLBL).

Methods:
We retrospectively reviewed medical record of the patient.

Results:
A 39-year-old woman visited the hospital for left facial pain and sensory impairment caused after the extraction of left maxillary wisdom tooth three months ago. In neurological examination, there was hypo-esthesia and pain in the V2 and V3 area of left trigeminal nerve. The left periauricular area also had pain and complained of hearing loss in the left ear. As a result of further evaluation, there was a left infratemporal fossa area mass found on the brain MRI and biopsy was carried out on mass. The biopsy results were B-cell malignant lymphoma, and the FDG PET-CT results, found invasive to liver, pancreas and scapular bone. Biopsy was implemented in the invasive area of the liver and final diagnosed with high grade atypical B-lymphocytic infiltration, DLBL.

Conclusions:
Symptoms of having wisdom teeth removed were impressed to be trigeminal neuralgia due to inflammation or postoperative complications, but imaging showed mass and final diagnosis was diagnosed with DLBL. The diagnostic brain imaging of brainstem, skull base fossa and cranial foramen is important in cranial neuropathy.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Trigeminal neuralgia, neurovascular compression, schwannoma, Diffuse large B-cell lymphoma, DLBL

The Small Fiber Neuropathy – Symptom Inventory Questionnaire (SFN-SIQ) does not discriminate between patients with or without small fiber neuropathy.

Poster No:
P 275

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Introduction:
The diagnosis of small fiber neuropathy (SFN) presents challenges as the current diagnostic tools are time-consuming and only available in specialised medical centers. Therefore more widely available diagnostic tools are needed. The SFN-SIQ is a questionnaire that consists of 13 symptoms that occur in SFN. The use of this questionnaire as a reliable screening tool could offer a solution, as it is easy to use and widely available. Earlier studies tried to assess the diagnostic accuracy of the SFN-SIQ, but were limited by a small group of patients. This study aimed to assess the diagnostic accuracy of the SFN-SIQ in a large cohort.

Methods:
We analysed data from 2,493 patients of which 2,021 were diagnosed with SFN based on a combination of clinical examination, abnormal quantitative sensory testing and/or decreased intraepidermal nerve fiber density in skin biopsy.

Results:
The area under the ROC curve, comparing patient with and without SFN and their total SFN-SIQ score, is 0,601. This reflects a poor diagnostic accuracy of the SFN-SIQ identifying SFN.

Conclusions:
We conclude that the SFN-SIQ is inadequate in differentiating between SFN and no SFN. Nevertheless, other diagnostic tools should still be explored.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: Princes Beatrix Spierfonds. Grant number W.TR22-01

Keywords: SFN-SIQ, Small Fiber Neuropathy, Diagnostic accuracy

Neuropathic pain correlates with disease severity in multiple sclerosis: a laser-evoked potential study

Poster No:
P 276

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Introduction:
Pain in multiple sclerosis (MS) has a prevalence of 55-70%. However, the demographic and clinical characteristics of MS patients with neuropathic pain is currently unknown. Our goal is to determine clinical/paraclinical correlates of neuropathic pain in an MS cohort.

Methods:
Twenty MS patients with chronic pain were included. Pain pathway was assessed by laser-evoked potentials (LEP) by Nd:YAG applied to the hand and foot dorsum. Somatosensory evoked potentials (SEP) of the median/tibial nerve were applied to assess the lemniscal pathway. Pain questionnaire (DN4), fatigue scale (FSMC), disease severity score (EDSS) and depression/anxiety scale (HAD) were evaluated. Spearman correlation analysis was applied to compare LEP results with epidemiological data, disease and imaging variables.

Results:
Median age (SD) is 47 ± 9 years, 55% female. 14/20 have a relapsing remitting course, 2/20 a secondary and 4/20 a primary progressive form. At least one relapse in the last year was observed in 4/20. 18/20 patients on disease modifying treatment (DMT). Median EDSS is 3.0 ± 2 (SD) and disease duration (DD) of 10 ± 6 years. 9/20 and 14/20 patients presented abnormal hand and foot LEP, respectively. 13/20 and 17/20 show abnormal median and tibial nerve SEP, respectively. Spearman correlation coefficient show positive correlation between foot LEP and EDSS (r= 0.6, P=0.005), FSCM (r=0.4, p =0.04), N20 latency of median nerve SEP (r=0.5, p=0.03), P40 amplitude of tibial nerve SEP (r=0.6, p=0.01). Aching/soring features correlated with LEP (r=0.5, p=0.02). No correlation between LEP and disease duration (r=-0.2, p=0.4), years on DMT (r=-0.06, p=0.8), DN4 (r=-0.2, p=0.4), FSMC (r=-0.3, p=0.2), body-mass index (r=0.06, p=0.8), HAD anxiety score (r=-0.3, p=0.2).

Conclusions:
70% of MS patients with pain showed dysfunction of the spinothalamic pathway. Neuropathic pain in MS presents with an aching/soring feature. LEP correlated the best with disease severity, fatigue score and SEP. However, no correlation was found with DN4 neuropathy score.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: Fondation Carlos et Elsie De Reuter

Keywords: pain, laser evoked potentials, neuropathic pain score, electrophysiology, SEP

Validation of neurofilament as a marker for neuropathic pain in the patients with diabetic polyneuropathy

Poster No:
P 277

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Introduction:
Pain in diabetic polyneuropathy is one of complaints for patients. However, the severity of pain cannot be graded objectively. The neurofilament light chain is widely used for assessment of axonal damage in neuronal system. We tried to validate neurofilament as marker reflecting pain severity in diabetic polyneuropathy.

Methods:
We enrolled the patients with diabetic polyneuropathy. The concentration of neurofilament light chain from serum was measured by single molecular array. Pain severity were evaluated by pain-DETECT and brief pain inventory. Also, the laboratory results including serum creatinine, HbA1C, and GFR. The correlation test was used to analyze each variable.

Results:
43 patients were enrolled. The concentration of neurofilament light chain was not able to reflect current severity of neuropathic pain. However, high level of neurofilament light chain was a significant predictor of poor control of diabetes ($r = 0.41$, $p = 0.02$) and kidney damages ($r = 0.45$, $p = 0.01$).

Conclusions:
Serum level of neurofilament light chain could not reflect current pain severity, but was highly associated with kidney dysfunction and poor control of diabetes. Other biomarkers needs to be elucidated to predict the pain severity and the makers for kidney dysfunction can be used for assessing the axonal damages in the patient with diabetes.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: diabetic polyneuropathy, neurofilament

SUDOSCAN As An Effective Tool For The Diagnosis Of Diabetic Neuropathy In An African Cohort

Poster No:
P 278

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Introduction:
The SUDOSCAN is an emerging tool for rapid and reproducible assessment of diabetic polyneuropathy (DPN). Studies have shown racial variations in small fiber function but data assessing the utility of the SUDOSCAN in african populations is scarce. We aim to evaluate the utility of SUDOSCAN for the diagnosis of DPN compared to the gold standard electrophysiological assessment in an african cohort

Methods:
Patients were consecutively recruited from the diabetic neuropathy clinic of Jordan Medical Services, Yaoundé, Cameroon between February 2022 and January 2023. DPN was assessed using the Toronto Clinical Neuropathy score, the vibration perception treshold and nerve conduction study (NCS). ESC of hands and feet neuropathy were measured with the SUDOSCAN. DPN was defined as pathologic NCS. The Independent T test was used to calculate difference between means and p values < 0,05 were considered significant.

Results:
A total of 71 patients were included (96% type 2, 2.7% glucose intolerance and 1.3% type 1). Mean age was 57.85± 10.79. The Male/female sex ratio was 1.9:1. Mean HbA1c was 7.82±1.92. Mean ESC scores were. 60.07±14.57 and 61.27±12.93microsiemens for feet and hands respectively. The prevalence of (electromyographic) DPN was 46.5%. Mean ESC scores were significantly lower between the DPN and No DPN sub groups only at the feet (55.39±16.49 vs 64.13±11.40 microsiemens respectively, p = 0.013). Considering a treshold of 60microsiemens for feet and 50 microsiemens for the hands, the SUDOSCAN wrongly classified only 10/71 (14.1%) as false negatives. Close to 70% (23/33) with pathologic NCS equally had abnormal feet and/or hand ESC.

Conclusions:
ESC measured by SUDOSCAN appears to be a rapid, simple and effective tool for the diagnosis of DPN compared to NCS in the african populations. It could be used for routine screening in diabetic clinics

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Diabetic Neuropathy, SUDOSCAN, Nerve Conduction Study

A New Integrated Approach for the Evaluation of Small Nerve Fibers

Poster No:
P 279

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Introduction:
Diagnosing small fiber neuropathy (SFN) remains a challenge due to relevant limitations of current tests, including skin biopsy and Sudoscan. Recently, a surface electrode for small fiber-selective stimulation was developed. Its specificity relies on an interdigitated micropattern with the conductive leads spaced 150 micrometers (150IDE) and alternately connected to opposite stimulator poles; this cathode-anode distance generates an electric field with a maximum skin depth of 100 micrometers, thus selectively activating the intraepidermal nerve endings. It allows the assessment of the nociceptive system through Nociceptive Evoked Potentials (NEPs) recorded from the scalp.

Methods:
We hereby propose a protocol for SFN diagnosis and monitoring that integrates Sudoscan and 150IDE-NEPs. We also aim to compare the reliability of the two methods and define the 150IDE-NEPs sensitivity in the early recognition of SFN. The protocol will be proposed to outpatients affected by neuropathy caused by type two diabetes, Charcot-Marie-Tooth disease type 1A (CMT1A), and hereditary transthyretin amyloidosis (hATTR), including hATTR pre-symptomatic carriers. Healthy controls matched by age and sex will be also studied with 150IDE-NEPs and Sudoscan. Patients with different neuropathies or skin diseases/lesions which may affect the 150IDE-NEPs will be excluded.

Results:
During the first visit, medical history will be collected, dysautonomia symptoms reported and quantified using Compound Autonomic Dysfunction Test and Composite Autonomic Symptom Scale-31, and a neurological examination, electroneurography, and Sudoscan performed. On another day, patients will undergo the 150IDE-NEPs test. Neurological examination with questionnaires, Sudoscan, and 150IDE-NEPs test will be repeated every 6 months.

Conclusions:
Since the 150IDE allows a low-cost evaluation of small fibers using standard electromyographic material, confirming its reliability in early SFN detection is important. SFN diagnosis could have therapeutic implications, for example by identifying early conversion to symptomatic disease in hATTR carriers.

References:
Yes

References 1:
M. Leandri et al.: Micropatterned surface electrode for massive selective stimulation of intraepidermal nociceptive fibres. Journal of Neuroscience Methods 293 (2018) 17–26.

References 2:

References 3:

References 4:

Grant Support:

Keywords: Small fiber neuropathy, Nociceptive Evoked Potentials

A Case Of Mononeuropathy In A Young Male Due To Common Peroneal Nerve Compression

Poster No:
P 280

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Introduction:
Common Peroneal Nerve Compression may be caused by trauma to the knee, fibula fractures or long repetitive periods of crossing of legs.

Methods:
We present a 19 year old male, who presented with a four-month history of progressive left leg numbness, associated with foot drop. He had no family history of a similar complaint. He had no known chronic diseases. He however had a habit of crossing his legs whenever he was seated for prolonged periods over the past 5 months Physical examination revealed a young healthy-looking male with a thin build, normal mental state and speech. There were no cranial nerve palsies and muscle bulk was normal. Tone was decreased in the left lower limb. Power in the upper limbs, hip extension, abduction and adduction bilaterally were 5/5. Plantar flexion and dorsi-flexion in the right were 5/5 while dorsi-flexion in the left was 2/5. Foot eversion was 5/5 on the right but 1/5 on the left. Foot inversion was 5/5 bilaterally. Deep tendon reflexes and planter reflexes were normal bilaterally. Sensation was reduced at left lateral calf and the dorsum of the foot. There was absent sensation in the left web space of the great toe. Tinel sign was positive at the fibula neck

Results:
NCS showed conduction block of the left common peroneal neck across the fibula neck.The rest of the NCS did not show signs of hereditary neuropathy with liability for pressure palsies

Conclusions:
Compression mono-neuropathy, such as that of the peroneal nerve at the fibula neck in our patient, may be a result of abnormal sitting posture in a young thin individual

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Common Peroneal Nerve Compression, Neuropathy, Foot drop

Multimodal MRI Uncovers Brain Damage in Hereditary Transthyretin Amyloidosis with Polyneuropathy

Poster No:
P 281

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Introduction:
Brain involvement is poorly studied in hereditary Transthyretin Amyloidosis with polyneuropathy (ATTRv-PN). Therefore, we sought to determine the pattern of brain grey (GM) and white matter (WM) involvement in ATTRv-PN using multimodal quantitative MRI in pre-symptomatic and symptomatic patients.

Methods:
We evaluated 39 patients (twenty-one symptomatic and eighteen pre-symptomatic) and 39 matched controls. They underwent MRI on a 3T PHILLIPS-Scanner. Freesurfer software was used to measure cortical thickness and deep GM volumes. Tract based spatial statistics (TBSS) algorithm was used to evaluate WM, using maps of fractional-anisotropy (FA), mean-diffusivity (MD), radial-diffusivity (RD) and axial-diffusivity (AD). All analyses were corrected for multiple comparisons. P-values<0.05 were deemed significant.

Results:
Mean age of symptomatic and pre-symptomatic patients were 52.4±16 and 38±10 years, respectively. In the symptomatic group, decreased FA was found predominantly in the cingulate and superior frontal gyri. MD, AD and RD were all increased in the cingulate and superior frontal gyri, in the cerebellum and occipital WM. These WM microstructural changes were predominantly left-sided. In the pre-symptomatic group, MD was increased in the frontal gyrus; AD and RD were increased in the cingulate gyrus and insular lobe. Cortical thinning was noticed predominantly in the left medial frontal (p=0.0027), left middle occipital (p=0.006), left superior temporal (p=0.0035) and right cingulate cortices (p=0.009) in symptomatic patients, and predominantly in the left and right hippocampal gyrus (p=0.026), right temporal pole (p=0.001) and left temporal pole (p=0.001) in pre-symptomatic patients.

Conclusions:
Brain damage is a counterpart of ATTRv-PN since early disease stages and should be evaluated in all affected subjects. MRI is able to detect brain damage in the disease, which may have clinical and therapeutic implications.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Hereditary Transthyretin Amyloidosis, MRI

EPIDEMIOLOGY OF PATIENTS WITH VAPB MUTATION AND MOTOR NEURON DISEASE - FUNCTIONAL IMPAIRMENT AND AUTONOMIC DYSFUNCTION

Poster No:
P 282

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Introduction:
Motor neuron diseases comprise conditions that are associated with progressive degeneration of both or either one of the motor neurons. First described in the late 19th century by Charcot, amyotrophic lateral sclerosis (ALS) is sporadic in almost 90% of the cases and is traditionally understood as a disease restricted to the motor neurons. This concept, however, is changing, and nowadays even familial forms are more frequently understood as a multisystemic disorder. In a previous study, we observed that VAPB-associated disease may have an underestimated important autonomic component. The main goal of this study is to disclose the epidemiological profile of our VAPB patients, highlighting the presence of dysautonomia.

Methods:
Between January 2021 and January 2023, we established remote contact with 51 patients and applied both ALS-FRS-R and COMPASS 31 scales. Whilst the former evaluated function impairment related to the condition, the latter searched for autonomic dysfunction by assessing orthostatic intolerance, vasomotor, secretomotor, gastrointestinal, bladder, and pupillomotor domains.

Results:
The mean age of our patients was 51.2 years, while the median age of onset was 43.2 years, with range from 37 to 65 years. 62,7% were female, and 58.8% had other chronic diseases, among which hypertension, diabetes, and hypothyroidism. The mean ALSFS-R score was 34.8. All but one patient described autonomic features, and median COMPASS 31 score was 20.49. 49% of the patients reported sexual dysfunction. Regarding dysautonomia, gastrointestinal manifestations were the most common (90.1%), followed by affected bladder (74.5%) and secretomor (66.6%) domains.

Conclusions:
VAPB mutation disorders seem to be associated with significant autonomic manifestations. Detailing these manifestations will bring more understanding of the disease and better patient care.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Motor neuron disease, VAPB gene, Dysautonomia, Amyotrophic lateral sclerosis, Spinal muscular atrophy

Molecular Mechanisms Of Perineural Invasion In Pancreatic Adenocarcinoma

Poster No:
P 283

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Introduction:
Perineural invasion (PNI) is a key event at the basis of tumor dissemination, especially in pancreatic ductal adenocarcinoma (PDAC). During PNI, cancer cells invade nerves and migrate along them, establishing a special microenvironment that promotes cancer growth and neural remodeling. PNI has a prevalence up to 100% in PDAC, is associated with early recurrence and poor prognosis and, to date, there are no available therapies targeting it.

Methods:
To clarify the molecular mechanisms governing PNI and the reciprocal interactions between PDAC and nervous cells, we replicated PNI in vitro, exploiting primary Schwann cells – DRG cocultures and murine K8484 PDAC cells. This model allowed us to characterize the crosstalk between PDAC and neuronal cells. Further, to evaluate more extensively these interactions and the involvement of PNI in tumor formation, we developed spheroids from K8484 cells, orthotopically transplanted them in murine pancreata and followed tumor progression.

Results:
Our in vitro results showed that K8484 cells affect myelin stability by both paracrine signaling and direct interactions. Interestingly, we identified a cancer-derived factor as a molecule responsible for myelin degeneration. Indeed, both inhibition of its downstream signaling in myelinated cocultures and ablation of its expression in cancer cells rescued myelin degeneration. Notably, human PDAC cells highly express this protein in invaded nerves. Thus, we characterized the role of this factor in tumor development, generating knocked-out K8484 cells and deriving spheroids from control and null cells. Orthotopic transplantation of these spheroids in vivo showed that, unlike controls, null spheroids developed smaller tumors in absence of metastatic events, confirming a crucial role for this protein in PDAC growth and spreading.

Conclusions:
In this study, we partially clarified the molecular mechanisms at the basis of PNI in PDAC and identified a specific molecule promoting tumor progression and dissemination that could potentially become a new therapeutic target in PDAC affected patients.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Perineural invasion, Pancreatic cancer, Neural remodeling, Nerve damage

Impact Of Hypoxia On Small Fiber Neuropathy In A Mouse Model Of Fabry Disease

Poster No:
P 284

Authors:
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Introduction:
Fabry disease (FD) is a lysosomal storage disorder caused by variants in the gene alpha-galactosidase A (GLA), which leads to impaired GLA enzyme function. As part of a multiorgan disorder, small fiber neuropathy (SFN) and pain are early symptoms of FD patients. While the mechanism of FD pain remains elusive, hypoxia may be a pathophysiological contributor. We hypothesize that hypoxia at the level of the dorsal root ganglia (DRG) contributes to alterations of neuronal ion channel expression and local angiogenesis, which lead to FD pain.

Methods:
We used the GLA knockout (KO) mouse model of FD to investigate hypoxia- and angiogenesis-associated markers on protein and gene expression level. We assessed 10 µm-cryosections of DRG from young (<6 months) and old (>12 months) GLA KO and wildtype (WT) mice. We performed immunofluorescent (IF) and qRT PCR analysis. IF analysis of CD31-positive blood vessels was performed to study DRG vascularization.

Results:
Cytosolic protein expression of the hypoxia-sensing molecule HIF1a was lower in DRG of young ($p<0.05$) and old GLA KO ($p<0.01$) compared to WT littermates. Nuclear measurement of HIF1a in DRG neurons showed higher intensity in old GLA KO compared to WT mice ($p<0.01$). In DRG neurons, protein expression of CA9, a downstream target of HIF1a, was higher in old GLA KO compared to WT mice ($p>0.01$). DRG gene expression levels of further selected hypoxia and angiogenesis markers did not differ between groups ($p>0.05$). Assessment of CD31-positive blood vessel density revealed higher vascularisation in DRG of old GLA KO compared to WT mice ($p<0.05$).

Conclusions:
Our data point to a hypoxic environment and increased vascularization in DRG of GLA KO mice, which may potentially contribute to ion channel dysregulation, neuronal apoptosis, and cellular stress.

References:
Yes

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Grant Support: SFB1158 Heidelberg Pain Consortium

Keywords: Fabry Disease, Hypoxia, Angiogenesis, Neuropathic Pain

A Case of Posterior Interosseous Nerve Palsy Resulting from Parosteal Lipoma of the Proximal Radius

Poster No:
P 285

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Introduction:
Ultrasound and MRI are the most commonly used methods for visualizing peripheral nerves. MRI and ultrasound each have unique advantages and limitations for imaging nerve pathology.

Methods:
A 74-year old woman presented with several months history of progressive weakness of right hand. The wrist extension was MRC grade 4 and finger extension was MRC grade 3. Sensation was intact.

Results:
Nerve conduction study revealed abnormal findings suggestive of posterior interosseous nerve palsy. Ultrasound revealed a solid well-demarcated hyperechoic mass located close to the radial cortex. Transverse view showed hypoechoic swelling of the posterior interosseous nerve just proximal to the supinator muscle. T1-weighted MRI showed a well-marginated homogeneous hyperintense mass. The appearance is highly suggestive of parosteal lipoma of the radius. She was diagnosed with posterior interosseous nerve palsy due to parosteal lipoma of the proximal radius.

Conclusions:
Advantages of ultrasound for detecting peripheral nerve pathology include higher spatial resolution, imaging of the nerve in continuity, and ease of side-to-side comparisons. Advantages of MRI over ultrasound include superior contrast resolution and imaging of structures that are deep or surrounded by bone. Therefore, ultrasound may better detect subtle changes in nerve caliber and MRI may better detect surrounding soft tissue abnormalities.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Ultrasonography, Magnetic Resonance Imaging, Mononeuropathies

Cognitive and behavioral functioning in painful small fiber neuropathy patients

Poster No:
P 286

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Institutions:
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Introduction:
Objective: Small fiber neuropathy (SFN) is a chronic pain condition with estimated prevalence of 53 cases per 100,000, causing severe individual and societal burden. While mood disorders have been described, the cognitive and behavioral profile of SFN patients has not been investigated.

Methods:
Methods: Thirty-seven painful SFN patients underwent comprehensive cognitive, behavioral, psychological, quality of life (QoL) and personality assessment using validated questionnaires. As control samples, we enrolled 38 patients with painful peripheral neuropathy (pPN) of mixed etiology and 30 healthy individuals (HC). Self-reported pain intensities at the time of assessment (NRS) and 4-week-average pain intensity (NRS-4) were registered. Between-group analyses (Kruskal-Wallis test) and Spearman correlations were performed.

Results:
Results: SFN and pPN showed similar cognitive profiles characterized mainly by reduced psychomotor speed ($p<0.05$ vs HC). Compared with HC, SFN reported severer subjective cognitive impairment, whereas PN had lower performances at attentive and naming tasks ($p<0.05$). Both groups showed significantly altered mood, high levels of catastrophism, and poor QoL ($p<0.002$ vs HC). But, compared to HC, only SFN showed higher levels of anxiety, alexithymia, and fatigue ($p<0.002$). Personality assessment revealed somatization and worthlessness feelings in SFN and pPN ($p<0.002$ vs HC). No differences in self-reported pain intensities were found between SFN and pPN. Correlations evidenced that mood and catastrophism were associated with NRS and NRS-4, fatigue with NRS-4, and feelings of worthlessness with NRS ($p<0.002$).

Conclusions:
Discussions: Although SFN reported subjective cognitive impairment, our results suggest that they had a normal-like cognitive profile, except for reduced psychomotor speed. The SFN behavioral profile is characterized not only by mood disorders but also by poor QoL, fatigue, alexithymia, and maladaptive coping strategies, as other chronic pain conditions, possibly related to pain intensity. Personality assessment suggests that somatization and worthlessness feelings, which may worsen the neuropsychological profile, deserve clinical attention when considering patients' therapeutic approaches.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Neuropsychology, Personality, Pain, Small fiber neuropathy, Painful peripheral neuropathy

Sensory Paraneoplastic Neuropathy as the First Manifestation of the Small-Cell Lung Carcinoma

Poster No:
P 287

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Introduction:
Sensory neuropathy is the typical form of the paraneoplastic peripheral neuropathy which may precede the onset of cancer for several years. It most often occurs in lung cancer, but also in other types of cancer (hematological, gastrointestinal tract or gynecological malignancies, unkonown primary malignancies). We report a case with sensory neuropathy and small-cell lung cancer.

Methods:
A 48-year old female patient gradually developed tingling and pain in her feet, and later in her lower legs and hands. The gait became unstable. She lost 10 kg over the period of six months and was admitted to the hospital.

Results:
Neurological examination: 'glove and stocking' distribution of sensory symptoms (pain, tingling), pseudoathetosis of upper limbs, areflexia, unstable gait. Electromyoneurography: moderate axonal, symmetrical sensory neuropathy of the upper and lower limbs, slightly more pronounced in the lower limbs. Anti-Hu antibodies: positive. Detailed examination (blood tests, cerebrospinal fluid, urine, internal organs) including whole-body FDG-PET/CT tomography excluded other types of neuropathy, drawing the attention to the paraneoplastic etiology, however the primary malignancy hasn't been revealed. She was treated with corticosteroids and gabapentin, with a mild reduction in symptoms. After two months whole-body FDG-PET/CT: multiple foci of intense pathological fluorodeoxyglucose accumulation in the mediastinal lymph nodes. Mediastinoscopy and biopsy of the lymph nodes: small-cell lung cancer. She was treated with cytotoxic drugs and gabapentin. At the beginning sensory symptoms and gait improved, but further on her condition worsened and she died a year after the neuropathy was diagnosed.

Conclusions:
Paraneoplastic neuropathy may precede a cancer for several years. It requires a detailed workup in the revealing the site of the primary malignancy (most often lung cancer) before the appropriate treatment could be initiated.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: paraneoplastic neuropathy, small-cell lung cancer

Pharmacological Modulation of HCN Channels Activity Decreases Oxaliplatin-Induced Peripheral Neuropathy Symptoms.

Poster No:
P 288

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Introduction:
Peripheral neuropathy, a common dose-limiting adverse effect induced by oxaliplatin (OIPN) is responsible of disabling symptoms, including distal or perioral paresthesia induced by cold. To date, no symptomatic treatment is available leading to an unmet medical need. Acute neuropathic pain symptoms have been correlated with overexpression of hyperpolarization-activated cyclic nucleotide channels (HCN) in dorsal root ganglion (DRG) and trigeminal ganglion (TG) neurons from oxaliplatin-treated mice. Moreover, HCN blockers have been shown to reverse oxaliplatin-induced cold hypersensitivity in mice. Though, in the absence of selective blockers, the potential cardiac side effects jeopardize the development of this pharmacological strategy. Alternatively, modulating HCN channel expression could be a new approach to reduce symptoms by targeting its interaction with TRIP8b, an auxiliary protein known to regulate the surface expression and/or function of the channel. Interestingly, the absence of TRIP8b in the heart suggests that our strategy should not induce any cardiac effect.

Methods:
We first aimed to confirm HCN isoforms/TRIP8 transcripts and proteins levels/co-localization in DRG and TG neurons from acute OIPN mice with RNAscope fluorescent multiplex assays, western-blot and immunocytochemistry. Secondly, we evaluated in these mice the pharmacological efficacy of newly designed peptoids targeting HCN-TRIP8b in electrophysiological and behavioral studies.

Results:
We show that HCN1, HCN2 and TRIP8b mRNA and proteins are highly colocalized in DRG and TG. As expected, we observe an increased Ih current density, specifically in small/medium sized DRG neurons from OIPN mice, that is significantly reduced after application of our lead peptoid compound without modifying the channel activation parameters. In vivo, we observe a dose-dependent antihyperalgic effect of our compound in OIPN mice, that is absent in TRIP8b KO mice.

Conclusions:
Overall, our results confirm that modulating TRIP8b-HCN interaction and thus HCN surface expression, is analgesic in a model of acute OIPN and that, contrary to non-selective HCN blockers, it does not affect cardiac function.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: This work was supported by the Agence Nationale pour la Recherche (ANR : PHARMHCN), the Institut National de la Santé et de la Recherche Médicale (INSERM), the Université Clermont Auvergne (i-site grant), the Region AURA (Pack Ambition Recherche : PeptHCN

Keywords: chemotherapy-induced peripheral neuropathies, HCN Channels, TRIP8b, Peptoids

Serum neurofilament light chain measurements following nerve injury

Poster No:
P 289

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Introduction:
Functional outcomes following Peripheral Nerve Injury (PNI) are dependent upon early recognition and prompt referral to specialist centres for appropriate surgical intervention. Technologies which facilitate the early detection of PNI would allow faster referral rates and encourage improvements in functional outcome. Serum Neurofilament Light chain (NfL) measurements are cheaper to perform, easier to access and interpret than many conventional methods used for nerve injury diagnosis such as electromyography (EMG) and/or MRI assessments. For the first time, this study determined whether the serum SIMOATM Neurofilament Light chain (NfL) assay can: 1) detect the presence of a nerve injury and 2) delineate between different severities of nerve injury.

Methods:
A rat sciatic nerve crush and common peroneal nerve crush were implemented as controlled animal models of nerve injury. At one, three, seven and 21 days post-injury, serum samples were retrieved for analysis using the SIMOATM NfL analyser kit. Nerve samples were also retrieved for histological analysis. Static sciatic index (SSI) was measured at regular time intervals following injury.

Results:
Approximately 45 and 20-fold increases in NfL serum levels were seen at one day post-injury following sciatic and common peroneal nerve injury respectively ($p<0.001$). This corresponded with an 8-fold higher volume of axons injured in the sciatic compared to common peroneal nerve ($p<0.001$). Serum NfL fold changes remained significantly ($p<0.05$) higher than baseline readings up to and including 7 days post-nerve injury in both injury groups. SSI measurements post-injury revealed reduced function at all time points in the sciatic crush group compared with the common peroneal crush group.

Conclusions:
NfL serum measurements represent a promising method for detecting nerve injuries. Clinical translation of these findings could provide a powerful tool to improve referral times for surgical management of nerve injured patients; consequently improvements in functional recovery may be seen.

References:
No

References 1:

References 2:

References 3:

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Grant Support:

Keywords: nerve injury, diagnosis, blood test

TREATMENT OF VOLATILE BLOOD PRESSURE IN A PATIENT WITH SPORADIC AMYOTROPHIC LATERAL SCLEROSIS

Poster No:
P 290

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Introduction:
Here we aimed to report a sporadic ALS case with highly volatile blood pressure (BP) and pulse rate (PR) that became stable after treatment with tamsulosin hydrochloride (HCL).

Methods:
Case Reports

Results:
A 63-year old female diagnosed as sporadic ALS 4 years before admitted to our hospital because of drastic BP changes. This began since 2 years ago. She had been prescribed calcium channel blockers (CCBs) and Angiotensin receptor blockers (ARBs) from other physician which was not effective at all. Her BP almost reached to 210/125 mmHg during the day and dropped down to 85/60 mmHg at dawn. Her PR was above 100 bpm almost all day and sometimes rose to 140 bpm. Work-up for secondary hypertension including abdominal CT and laboratory tests for hormones was negative. We tried doxazocin mesylate a long-acting alpha-1 adrenoceptor blocker first and found less effective for diurnal fluctuation, therefore, changed to tamsulosin HCL. It attenuated BP surge and maintained well after home discharge.

Conclusions:
Autonomic dysfunction had not been generally considered as main problems in patients with ALS. However, several evidences have been revealing that ALS is just not a disease of pure corticospinal tract and anterior horn cell system, especially in terms of affecting cognition and autonomic functions. Severe BP fluctuation and tachycardia can be one of ALS multi-systemic manifestations and it might be successfully manageable by tamsulosin HCL as in previous reports and our case. Good response to the alpha-adrenergic blocker but not CCBs or ARBs suggests the possibility of the ALS primarily affecting the sympathetic nervous system.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: sympathetic nervous system, sporadic amyotrophic lateral sclerosis

TNFR1 in oral cancer pain associated with perineural invasion

Poster No:
P 291

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Introduction:
Oral cancer patients suffer from pain that severely impairs oral function. Cancer invading the nerve (i.e., perineural invasion, PNI) is associated with more severe pain and impaired oral function in cancer patients. We previously showed that TNF, a potent proinflammatory and algogenic mediator, is concentrated in the tumor microenvironment and correlated with self-reported pain in oral cancer patients.

Methods:
Here we tested whether blocking TNF activation of TNFR1 could alleviate oral cancer pain and improve function in a mouse sciatic nerve model of PNI. We measured pain-like behaviors, motor functions, and conducted intracellular recordings in dorsal root ganglion cells in mice lacking TNFR1 or treated with a selective TNFR1 blocker xPro1595.

Results:
We found that PNI induced more severe mechanical allodynia and motor dysfunction in female mice. TNFR1 gene deletion or treating mice with xPro1595 alleviated mechanical allodynia and improved several measurements of motor function, including track length, toe-spreading, and time spent in running and trotting. Our electrophysiological data show that PNI results in a wide range of severe peripheral cellular pathologies consistent with our previous report. Briefly, both transduction and electrical activation patterns are disrupted in a modality specific manner in mice with PNI. Our preliminary data suggests an inverted sensibility between nociceptors and tactile afferents in mice with PNI. Nociceptors exhibited decreased mechanical thresholds and increased spontaneous activities, whereas tactile afferents exhibited increased mechanical thresholds to a point that some failed to respond to mechanical stimulation.

Conclusions:
We conclude that PNI-associated pain is neuropathic in nature and targeting the TNFR1 pathway may be a promising therapeutic approach to reduce pain and improve function.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: This work is supported by National Institutes of Health grants R01 DE029493 (Ye Y), R01DE032501 (Ye Y), and Department of Defense (DoD) CP210088P1 (Ye Y).

Keywords: Head and neck cancer, neuropathic pain, oral cancer, perineural invasion, nociceptor sensitization

Median Nerve to Ulnar Artery Cross-sectional Area Ratio: Diagnostic Tool for Carpal Tunnel Syndrome

Poster No:
P 292

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Introduction:
Recent studies have found the changes in cross-sectional area (CSA) of ulnar nerve in carpal tunnel syndrome (CTS) patients and the after trans-carpal release operation. The carpal tunnel is located near the Guyon canal, and increased pressure in the carpal tunnel might affect the ulnar nerve in the Guyon canal at the wrist. Therefore, ultrasonographic parameters related to ulnar nerve can lead to ambiguous result of evaluation. The aim of this study is to identify the value of the parameters including ulnar artery related aspects in CTS patients.

Methods:
In this study, twenty-nine newly diagnosed CTS wrists were recruited. They have no surgical history or treatment history before and the diagnosis was fully based on electromyography. Also, nineteen normal wrists with health volunteers participated in this study. We measured the median nerve and ulnar nerve in three level, including carpal tunnel inlet, carpal tunnel outlet, and 12cm proximal from wrist crease. We also evaluate the CSA of ulnar artery at the moment of fully dilated state in same three levels. Using these parameters, at all three levels, we obtain the several diagnostic parameters which are well-defined as CTS ultrasonographic findings. Furthermore, MUAR of each level was collected for analyzing the difference between CTS patients and normal population.

Results:
The CSAs of median nerve at carpal tunnel inlet and outlet level were statistically significantly larger in the CTS group than control group. Also, the MUAR at 12cm proximal from wrist crease was statistically significantly smaller in the CTS group than control group. In addition, wrist to forearm ratio (WFR) of median nerve CSA was statistically significantly smaller in the CTS group than control group.

Conclusions:
In this study, we additionally found that MUAR at forearm level is as useful as other parameters which has been proven in previous studies as a meaningful diagnostic ultrasonographic value of CTS.

References:
No

References 1:

References 2:

References 3:

References 4:

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Keywords: Carpal tunnel syndrome, Ultrasonography, Diagnosis

Neurophysiological findings of 747 patients underwent carpal tunnel surgery

Poster No:
P 293

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Introduction:
Carpal tunnel syndrome (CTS) is a common disease, and surgery is performed if it does not respond to medication and conservative treatment. We aimed to describe the results of neurophysiological study and clinical characteristics of patients with carpal tunnel release.

Methods:
The medical records of 747 CTS (female 620, male 127) patients were retrospectively reviewed. Neurophysiological results (nerve conduction studies), tinel signs, Phalen test, duration of symptoms, thenar muscle atrophy, steroid injection, and past medial history were investigated. According to the neurophysiological results, the severity of CTS was classified from 0 to 6.

Results:
There were 127 male and 620 female, and their average prevalence of symptoms was 32±47.3 months. 270 people underwent surgery on their right wrist, 208 on their left wrist and 195 on both wrists. Tinel signs were 80% positive, 68% for the Phalen's test, and 28% for thenar muscle atrophy. 16% of patients underwent steroid injection prior to surgery. According to the CTS grade criteria, there were 18 for the grade 6, 56 for the grade 5, 24 for the grade 4, 158 for the grade 3, 13 for the grade 2, 2 for the grade 1, and 17 for the grade 0. The nerve conduction results of median nerve (terminal latency, compound muscle action potential amplitude, motor NCV, sensory nerve action potential amplitude, and sensory NCV) is shown in the table.

Conclusions:
This study describe the clinical characteristics and nerve conduction test results of 747 patients underwent carpal tunnel release. The symptom period before surgery is about 32 months. 16% received steroid injections about 1 to 3 procedures. Most of the patients are operated at NCS CTS grade 3.

References:
No

References 1:

References 2:

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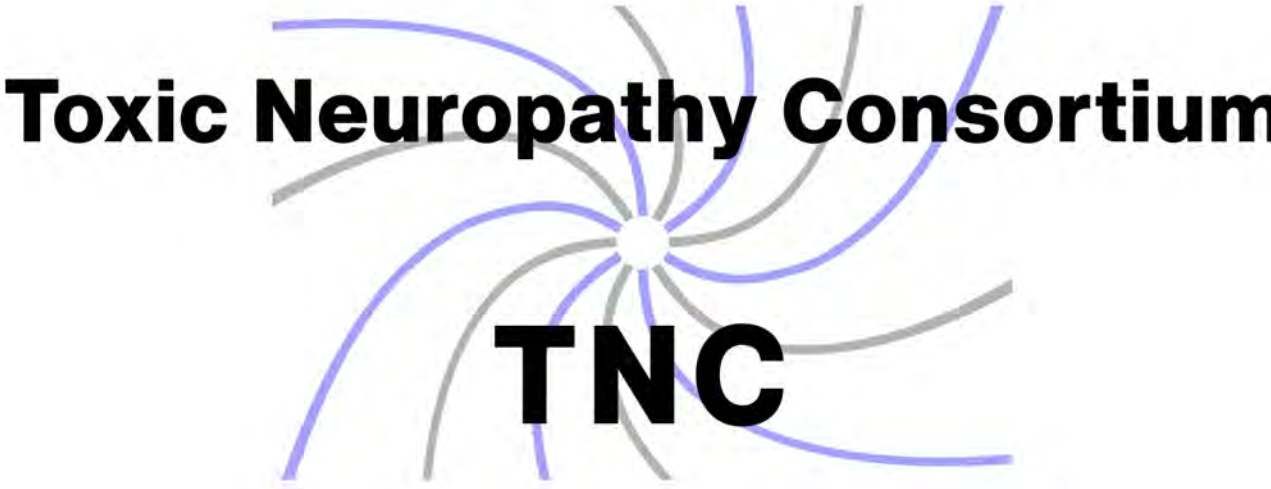
Grant Support: none

Keywords: Carpal tunnel syndrome, Neurophysiologic , nerve conduction study



Toxic Neuropathy Consortium (TNC) Abstracts

P 294 - 325

Ablation Of All Monocarboxylate Transporters Selectively From Schwann Cells Delays Peripheral Nerve Regeneration

Poster No:
P 294

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Introduction:
Monocarboxylate transporters (MCTs), specifically MCT1, MCT2, and MCT4, are the primary transporters for lactate, pyruvate and ketone bodies in Schwann cells. These transporters have been shown to play critical roles in many cellular processes, including metabolism, myelination, and peripheral nerve regeneration. Our laboratory and others have previously shown that removing MCT1 alone from Schwann cells leads to hypomyelination, disrupted lipid metabolism, and reduced motor end-plate innervation. Surprisingly, we found that selective ablation of MCT1 from Schwann cells did not impact nerve regeneration. Since Schwann cells also express MCT2 and MCT4, our hypothesis is that these two closely related transporters are able to partly compensate for the loss of MCT1.

Methods:
To assess the role of all MCTs, we obtained mice with selective ablation of MCT1, MCT2, and MCT4 from Schwann cells, termed P0-Cre:MCT TripleFlox mice. These mice do not develop peripheral nerve abnormalities, at least during young adulthood. P0-Cre:MCT TripleFlox mice and littermate controls (i.e., WT:MCT TripleFlox mice) underwent sciatic nerve crush and recovery was followed for six weeks by electrophysiology, behavior studies, and histology

Results:
By electrophysiology, there was incomplete recovery of conduction velocity, with the maximum recovered conduction velocity being 56.5% of pre-crush values in P0-Cre:MCT TripleFlox mice, as compared to 78.6% in WT:MCT TripleFlox mice ($p<0.05$). Impaired recovery was also seen by behavior, with significantly impaired recovery of toe spread index ($p<0.0001$) and horizontal ladder walk ($p<0.01$), and histology, with significantly reduced neuromuscular junction (NMJ) reinnervation (56.2% NMJ fully reinnervated in P0:MCT1 TripleFlox compared to 80.4% in WT:MCT1 TripleFlox; $p<0.01$).

Conclusions:
Our findings demonstrate that knockout of all MCTs from Schwann cells impairs the capacity of peripheral nerves to regenerate. Given prior publications demonstrating the importance of Schwann cell-axon communication for peripheral nerve regeneration, our study suggests the importance of MCTs in the metabolic coupling between Schwann cells and axons.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: NIH R01NS086818

Keywords: Nerve regeneration, Metabolism, Monocarboxylate transporter, Schwann cell, Mouse model

Netazepide, an antagonist of cholecystokinin type 2 receptor, prevents paclitaxel-induced sensory neuropathy in mice

Poster No:
P 295

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Introduction:
Paclitaxel (PTX)-induced peripheral neuropathy (PIPN) is a frequent adverse effect affecting around 70% of PTX-treated patients. An up-regulation of cck2r gene, coding for the cholecystokinin type 2 receptor (CCK2R) was observed in dorsal root ganglia (DRG) in our model of PIPN. CCK2R, is expressed in central and peripheral nervous system, and involved in nociceptive process. Hence, our aim was to investigate the effect of CCK2R blockade on the onset of PIPN using the CCK2R antagonist, netazepide (NTZ, Trio Medicine Ltd.), currently in phase II clinical trial for gastric neuroendocrine tumors.

Methods:
PTX was injected intraperitoneally in Swiss mice every other day during 8 days at 2 mg/kg. NTZ was administrated per os starting one day before and until the end of PTX treatment, at 2 mg/kg/d. Tactile sensitivity and thermal (hot/cold) nociception were assessed at reference day before the first PTX injection (day 0) until day 13. At the end of the treatment, immunohistochemistry and morphological analyses were performed on DRG, skin biopsies and sciatic nerve. In vitro, the effect of NTZ on PTX cytotoxicity was evaluated on two human cancer cell lines, using viability assay using NTZ at an incremental dose (0 to 20 nM) or in combination with PTX.

Results:
Our results showed that PTX induced significant tactile allodynia from day 5 to day 13, without significant modification of thermal nociception. PIPN was characterized by both DRG neurons and intraepidermal nerve fibers loss, and a decrease of unmyelinated and myelinated axons in the sciatic nerve. NTZ completely prevented the occurrence of tactile allodynia, and nerve injuries induced by PTX. In vitro, NTZ alone did not affect cell viability, nor the cytotoxic activity of PTX in both cell lines.

Conclusions:
The finding that NTZ protects against PTX-induced sensory neuropathy strongly supports the exploration of its neuroprotective potential for patients under chemotherapy.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: chemotherapy-induced peripheral neuropathy, paclitaxel, netazepide, CCK2R, neuroprotection

Chemotherapy-induced peripheral neurotoxicity: Socioeconomic impact on health-related quality of life, daily activities and employment

Poster No:
P 296

Authors:
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Introduction:
Chemotherapy-induced peripheral neurotoxicity (CIPN) is a frequent complication of cancer therapy which reduces treatment tolerability and leads to potentially persistent disability. However, the impact of CIPN on employment and daily functioning have been less explored and are essential to understand the social costs of persistent neuropathy.

Methods:
354 patients treated with neurotoxic chemotherapies (paclitaxel, docetaxel, oxaliplatin, cisplatin, bortezomib, vincristine) were assessed cross-sectionally 8.8 months post completion of treatment. CIPN was assessed via patient reported outcomes (EORTC-CIPN20), neurological grading scale (Total neuropathy score) and clinical grade (NCI-CTCAE). Health-related quality of life (HRQoL) was collected using the Assessment of Quality of Life (AQoL-8D). Patients reported employment and daily functioning on a standardized questionnaire. Regression analyses were used to investigate the association between CIPN and HRQoL, employment and daily functioning.

Results:
The majority of patients reported CIPN (81%,n=287) at the time of assessment. People with CIPN had significantly reduced HRQoL (overall AQoL-8D: CIPN 0.73 ±0.18, no CIPN 0.79±0.17, $p<0.05$) and reduced scores for subdimensions independent living, coping, super dimension physical and mental (all $p<0.05$) compared to those without CIPN. Results from linear regression showed that moderate to severe CIPN ($p<0.001$) and older age ($p<0.005$) were associated with reduced HRQoL score. While older people were less likely to have a paid job ($p<0.05$), having moderate to severe CIPN had a statistically significant negative impact on hours of paid work independent of age ($p<0.05$). People with moderate/severe neuropathy were more likely to require help with household tasks and assistance from a caregiver ($p<0.05$).

Conclusions:
CIPN has a significant impact on quality of life and daily functioning, with likely worse impact in older people. Support should be tailored to individuals with CIPN to improve function and facilitate daily activities. The socioeconomic impact of CIPN should be evaluated and considered in future studies examining cost implications of cancer therapy.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Chemotherapy induced peripheral neurotoxicity, CIPN, Quality of life, Function

Efficacy and Safety Phase 2 Study With Topical Amitriptyline in Chemotherapy-Induced Peripheral Neuropathic Pain in Adult Cancer Survivor Patients

Poster No:
P 297

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Introduction:
Chemotherapy-induced peripheral neuropathy (CIPN) is a common and challenging complication of antineoplastic agents. Dose reduction or premature cessation of chemotherapy due to severe pain may impact treatment efficacy and patient survival. Oral drug efficacy (antiepileptics or antidepressants) is generally considered as modest and accompanied by a significant risk of adverse events.

Methods:
Amitriptyline (AMT)'s mechanism of action on the peripheral nervous system was elucidated recently (different from its activity in the CNS). The ongoing phase II, randomized, double-blind, parallel arm study compare the efficacy and safety of ATX01 (10 or 15%) to placebo. Adult cancer survivor patients randomized to the study should have completed their CT treatment since at least 6 months, having a DN4 ≥ 4 and a NPRS ≥ 4 related to a prior course of platinum and/or taxane. The effects on other sensory symptoms, rescue medication use and on function/ Quality of life using validated scales (BPI-Short Form, European Organization for Research and Treatment of Cancer Chemotherapy-Induced Peripheral Neuropathy 20 (EORTC CIPN20) and Patient's Global Impression of Change (PGIC)) are secondary outcome measurements. 240 patients are necessary to statistically demonstrate the superiority of ATX01 over placebo. The study is conducted in 43 investigational sites in Europe (CTAs approved) and the USA (IND and Fast Track Designation granted).

Results:
AMT was found to be a potent inhibitor of Sodium Channels (Nav) and of sensory neurons. AMT significantly inhibits the activity of Nav 1.7, 1.8 and 1.9 and of the firing activity of A∂ and C fibers leading to alleviation of neuropathic pain. Phase 2 results should confirm the importance of such mechanism.

Conclusions:
In view of the mechanism of action of AMT, the topical administration of ATX01 directly on the painful sites (hands and/or feet) can directly have a significant impact on the peripheral sensory neurons without interfering with the CT treatment.

References:
Yes

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References 4:
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Grant Support:

Keywords: chemotherapy induced peripheral neuropathic pain, topical amitriptyline, clinical study, sodium channels and sensory neurons

Acute and chronic Oxaliplatin-induced peripheral neurotoxicity: two sides of the same coin.

Poster No:
P 298

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Introduction:
Oxaliplatin-induced peripheral neurotoxicity (OIPN) hampers quality of life of a relevant proportion of cancer survivors. OIPN is characterised by a peculiar profile, since acute and chronic syndromes can arise. Acute OIPN is related to the transient dysfunction of voltage-operated ion channels. Acute OIPN might influence chronic OIPN development: in fact, modulating the former, the latter can be prevented (ref.1,2).

Methods:
In this study we characterised acute and chronic OIPN in a rat model obtaining a time course of events related to both toxicities; to characterise acute OIPN we relied on nerve excitability testing (NET) and cold plate test. We compared a control group with a group treated with oxaliplatin for 1 month (n=10 each) and performed a 6 week follow-up after treatment completion. Both groups were studied with behavioural and neurophysiological (nerve conduction studies, NET) testing at baseline, end of treatment and 6 weeks after treatment. NET and cold plate test were also performed 24 hours after the first drug administration. We obtained histopathology (caudal nerve, skin biopsy, dorsal root ganglia) at the end of treatment and at 6 weeks of follow-up.

Results:
At 24 hours acute OIPN ensued in the treatment group. At the end of treatment all outcome measures showed that neuropathy had ensued in the treatment group. At 24 hours after the last administration acute OIPN was still present too. However, in the subsequent monitoring acute OIPN was not present anymore while chronic OIPN was still observed.

Conclusions:
We shed light on the time course of events related to acute and chronic OIPN. Acute OIPN, despite transient, can contribute to axonal damage. Our time course highlights the need to modulate acute OIPN as soon as the first chemotherapy cycle or, even better, before starting chemotherapy to prevent chronic OIPN.

References:
Yes

References 1:
Alberti P, Canta A, Chiorazzi A, Fumagalli G, Meregalli C, Monza L, Pozzi E, Ballarini E, Rodriguez-Menendez V, Oggioni N, Sancini G, Marmiroli P, Cavaletti G. Topiramate prevents oxaliplatin-related axonal hyperexcitability and oxaliplatin induced periph

References 2:
Ballarini E, Malacrida A, Rodriguez-Menendez V, Pozzi E, Canta A, Chiorazzi A, Monza L, Semperboni S, Meregalli C, Carozzi VA, Hashemi M, Nicolini G, Scuteri A, Housley SN, Cavaletti G, Alberti P. Sodium-Calcium Exchanger 2: A Pivotal Role in Oxaliplatin

References 3:

References 4:

Grant Support:

Keywords: CIPN, nerve excitability testing, neuropathology, nerve conduction studies, oxaliplatin induced peripheral neurotoxicity

Prevention Of Peripheral Neuropathy In Cancer Chemotherapy: Breaking The Microtubules By Ultrasound Neutralizes Paclitaxel Neuron Toxicity

Poster No:
P 299

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Introduction:
Paclitaxel (and other Taxane drugs) is a key drug used in several solid tumors including ovarian, breast, prostate, pancreas, and non-small cell lung cancer. Paclitaxel targets microtubules for the anti-cancer activity: the small molecules bind and suppress microtubule dynamics and stabilize the filaments. In doing so, paclitaxel triggers mitotic catastrophe and death of the cancer cells, but also causes neuronal damage. The collateral consequence is peripheral neuropathy, a dosage-limiting side effect for the full utilization of paclitaxel. The development of satisfactory methods to reliably prevent paclitaxel-induced neuropathy is an urgent, unmet medical need. We have made an unexpected discovery that a brief exposure to low intensity ultrasound can effectively neutralize the cytotoxic effects of paclitaxel on cultured cells by disrupting paclitaxel-induced rigid microtubule bundles. Therefore, we propose here to test whether low intensity ultrasound can prevent the peripheral neuron cytotoxicity of paclitaxel in zebrafish and mouse models.

Methods:
We proposed to test whether low intensity ultrasound can prevent the neuron cytotoxicity of paclitaxel in zebrafish and mouse models. We treated C57BL/6 mice with paclitaxel to induce peripheral neuropathy, and determined if local ultrasound exposure (4 to 6 hours after paclitaxel injection) can prevent paclitaxel-induced peripheral neuropathy in vivo. We analyzed the effects on the microtubule network and cell death, and study the lysosomal localization and degradation of paclitaxel-bound microtubule fragments generated following exposure to ultrasound in the mouse paws. The ability of low intensity ultrasound to remove paclitaxel neuronal toxicity was also demonstrated in zebrafish.

Results:
We found that a brief exposure to low density ultrasound waves was sufficient to eliminate paclitaxel cytotoxicity in neuronal cells in culture by transiently breaking microtubule filaments, which were then relocated to lysosomes for disposal.

Conclusions:
Ultrasonic force to break rigid microtubule is an effective antidote to counter paclitaxel cytotoxicity, which may have obvious clinical applications. Based on the laboratory results and mechanistic understanding, we conclude that low intensity ultrasound is sufficient and practical to prevent and reduce toxicity of cancer drugs on peripheral neurons. The scientific findings and understanding will guide a new and practical method to prevent neuropathy in cancer treatment, and will significantly contribute to survivorship issues and improve quality of life for cancer patients.

References:

No

References 1:

References 2:

References 3:

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Grant Support: Internal pilot funding from Sylvester Comprehensive Cancer Center/University of Miami was the key supported for this project. The lab was also partially supported by funds from grants R01 CA230916, R01 CA095071, R01 CA099471, R01 CA79716, and R01 CA23091

Keywords: Ultrasound, shock wave, microtubules, Taxol/Paclitaxel, peripheral neuropathy

Incidence and risk factors for developing chemotherapy-induced neuropathic pain (CINP)

Poster No:
P 300

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Introduction:
Introduction: Chemotherapy-induced peripheral neurotoxicity (CIPN) is mostly characterized by sensory abnormalities and proprioception changes, but burning sensations consistent with neuropathic pain due to affectation of small nerve fibers can also occur at significant rates (up to 35% of affected patients). Our aim was to define the incidence and risk factors for developing chemotherapy-induced neuropathic pain (CINP).

Methods:
Methods: We performed a retrospective analysis of cancer patients followed-up for CIPN with or without CINP at the participating sites. CINP was assessed by means of VAS and DN4 questionnaire, while TNSc was used to grade CIPN.

Results:
Results: A total of 453 CIPN patients with a mean age of 53.3±10.5 years were screened. 60.9% (n=276) were females. Patients received oxaliplatin (190; 41.9%), cisplatin (20; 4.4%); taxanes (187; 41.3%), combination paclitaxel and cisplatin (42; 9.3%) or other neurotoxic agents (14; 3.1%). CINP was found in 111 (24.5%) patients. The mean VAS at CINP first evidence was 4 (range 3-8) and 6 at the end of chemotherapy. CINP first appeared after a median of 3 chemotherapy cycles. The patients with the highest risk of developing CINP were those treated with combination of paclitaxel+cisplatin Odds ratio (OR): 7.1 ($p<0.01$), followed by paclitaxel OR: 5 ($p<0.01$) and then platinums OR: 4 ($p<0.01$). Patients receiving the chemotherapy schedules at full dose intensities OR: 1.7 ($p=0.01$) and those with preexisting well-controlled uncomplicated diabetes OR: 1.3 ($p=0.02$) were also more liable to manifest CINP.

Conclusions:
Conclusion: The incidence of CINP (24.5%) in our cohort was comparable to previous reports. Chemotherapy at full dose intensities with the combination use of two neurotoxic agent or paclitaxel monotherapy mostly increases the risk for developing CINP. Further prospective longitudinal studies are needed to identify different CINP phenotypes and risk factors to the development of CINP in order to inform clinical decisions towards improved management options.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Chemotherapy, Neuropathic pain, Chemotherapy-induced peripheral neurotoxicity , Chemotherapy-induced neuropathic pain , Risk factors

Exploratory Analysis for categorical Total Neuropathy Scale grading

Poster No:
P 301

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Introduction:
The assessment and interpretation of chemotherapy-induced peripheral neurotoxicity (CIPN) is challenging because it is commonly perceived differently by patients and physicians. The total Neuropathy Scale, clinical version (TNSc) provides more neurological details and has shown slight better clinimetric properties than the Common Terminology Criteria for Adverse Events (CTCAE). However, the categorization of this continuous scale in groups, according to the CIPN severity, is still poorly studied, hampering the making-decisions in clinical practice. Objective:To identify the relevant variables for defining the group of patients with or without clinically-significant CIPN.

Methods:
Two exploratory unsupervised clustering analysis were used (k-means or two-step Birch methods) using the TNSc items, alone or split by the sum score of symptoms (Sensory (S), Motor (M), Autonomic(A)) and signs (strength (S), reflexes (R), vibration (V) and pin (P) sensibility), coupled to the CIPN20 quality-of-life questionnaire scores obtained at the end of treatment in a prospectively assessed cohort of cancer patients.

Results:
One hundred-one patients, with a mean age of 57.38±11.28 years-old, were included. 52.5% were females. Patients received oxaliplatin (52.5%), taxanes (31.7%), or other neurotoxic agents (15.8%). Median TNSc was 6 (range:0-17), and neuropathy distribution according CTCAE was 13.9%,44.6%, 38.6% and 3% for no neuropathy, and grades 1 to 3, respectively. Clustering analyses shown most robust models using split than isolated TNSc items. K-means and 2-step methods identified 2 clusters with centroids located at 3.71 and 2.94 in SMA, at 5.88 and 5.54 in SRVP, and at 39.67 and 30.45 in CIPN20 for patients with and without relevant CIPN, respectively. Validation analysis and adaptation for practical purposes point out the k-means model as more accurate.

Conclusions:
Euclidean location in these defined clusters is an easy way to classify CIPN patients, but a larger confirmatory study with major proportion of high grade neuropathy patients according CTCAE is needed.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: chemotherapy-induced neurotoxicity, Total Neuropathy Scale, Quality of life

Peripheral neurotoxic medication in Charcot-Marie-Tooth (CMT) patients

Poster No:
P 302

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Introduction:
Several widely used medications are toxic to the peripheral nervous system. Concern exists about the use of these drugs in patients with pre-existing peripheral neuropathy such as those with inherited neuropathies.

Methods:
We performed a systematic review using the following PubMed search string: (drug name) AND ((charcot marie tooth) OR (hereditary neuropathy) OR (hereditary neuropathy with pressure palsies) OR (Charcot-Marie-Tooth) OR (CMT) OR (CMT1) OR (CMT2) OR (DI-CMT) OR (dHMN) OR (distal hereditary motor neuropathy) OR (Dejerine-Sottas syndrome) OR (hereditary sensory neuropathy) OR (hereditary sensory and autonomic neuropathy)). Drug name in the search string was based on the American Charcot-Marie-Tooth Association (CMTA) list of potentially neurotoxic medications.

Results:
Our results provide evidence-based support for the possibility that the use of vincristine and paclitaxel can occasionally induce an atypical, and more severe, course of drug-related peripheral neurotoxicity in CMT patients. However, no convincing evidence for a similar recommendation could be found for all the other drugs.

Conclusions:
Currently, vincristine and paclitaxel should be considered as higher-risk drugs in CMT vs non-CMT patients, but only prospective systematic collection of well-characterized series of CMT patients treated with established or putative neurotoxic drugs will provide definite evidence in favor or against a possible increased risk of peripheral neurotoxicity in this specific population.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: This study was supported by a Charcot-Marie-Tooth Association grant

Keywords: neurotoxic medicatons, CMT, neurotoxicity

A mouse model of sensory neuropathy induced by a long course of monomethyl-auristatine E treatment

Poster No:
P 303

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Introduction:
Antibody-drug conjugates (ADCs) are anticancer drugs consisting of a monoclonal antibody, targeting selective tumor antigens, to which has been frequently associated a highly potent cytotoxic agent, the Monomethyl Auristatin E (MMAE) using chemical linker. The MMAE is a tubulin polymerization inhibitor derived from dolastin-10. These MMAE-ADCs are responsible for peripheral nerve toxicities. Our objective was to develop and characterize a mouse model of MMAE-induced peripheral neuropathy induced by free-MMAE injections.

Methods:
MMAE was injected in Swiss mice at 50 µg/kg i.p. every other day for 7 weeks. Assessments of motor and sensory nerve functions were performed once a week on MMAE and Vehicle mice. Sciatic nerve and paw skin were removed at the end of experiment for subsequent immunofluorescence and morphological analysis.

Results:
MMAE did not affect motor coordination, muscular strength and heat nociception, but significantly induced tactile allodynia in MMAE mice compared with vehicle mice from day 35 to day 49. MMAE significantly reduced myelinated and unmyelinated axon densities in sciatic nerves and lead to a loss of intraepidermal nerve fibers in paw skin.

Conclusions:
In summary, MMAE induced a peripheral sensory neuropathy associated with nerve degeneration in our experimental conditions. This model is valuable as it brings the opportunity to study all MMAE-ADCs-induced peripheral neuropathies. Moreover, it may represent a useful tool to screen neuroprotective strategies.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Chemotherapy induced peripheral neuropathy, CIPN, Antibody-drug conjugate, Monomethyl Auristatin E, Model

Prevalence And Features Of Inflammatory Demyelinating Polyneuropathies Associated With Brentuximab-Vedotin Therapy: A Retrospective Cohort Study

Poster No:
P 304

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Introduction:
Peripheral neuropathies are frequent complications of Brentuximab-Vedotin (BV), an antibody-drug conjugate used in the treatment of CD30+ lymphoma. Their classical pattern (BV-CPN) is length-dependent sensory axonal neuropathy. Severe inflammatory demyelinating polyneuropathies (BV-IDP) have been described. BV-IDP contribute to the morbidity associated with lymphoma but may respond to immunotherapy. Our primary objective was to evaluate the prevalence of BV-IDP. Our secondary objectives were to determine potential risk factors and warning signs.

Methods:
We conducted a retrospective cohort study on all patients treated with BV at our centre, between April 2014 and July 2021. Clinical, biological, and electrophysiological data were collected. BV-induced neuropathies were defined as the occurrence of neuropathy up to 8 weeks after BV discontinuation. The 2021 EAN/PNS electrodiagnostic criteria for chronic inflammatory demyelinating polyneuropathies were used to identify BV-IDP. Other neuropathies were classified as BV-CPN.

Results:
Among 83 patients, 41 developed a neuropathy: 36 BV-CPN and 5 BV-IDP. The prevalence of BV-IDP was 6% among all patients treated with BV. No predisposing factor could be identified. Patients with BV-IDP presented more frequently with muscle weakness (60% vs 5,6%, $q<0,05$), gait disorders (100% vs 19%, $q<0,05$), prehension disorders (80% vs 22%, $q<0,05$), or subacute onset (60% vs 5,6%, $q<0,05$). BV-IDP were frequently more severe (CTCAE grade ≥ 3, 40% vs 2,8%, $q<0,05$). Using those red flags, three patients initially classified as BV-CPN were subsequently considered as uncertain BV-IDP but did not fulfil the 2021 EAN/PNS criteria. The prevalence of BV-IDP could then reach 9.6%.

Conclusions:
BV-IDP are frequent and probably underestimated. A close follow-up is essential to early detect them. Nerve conduction studies should be performed if the presence of the following red flags: subacute onset, muscle weakness, gait disorder, prehension disorder, or high severity. The presence of demyelinating features could lead to discontinuation of BV or initiation of immunotherapy.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: None

Keywords: Toxic neuropathy, Inflammatory demyelinating polyneuropathy

Pure autonomic failure and the Synuclein-One Study: The role of the peripheral nervous system in neurodegenerative disorders

Poster No:
P 305

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Introduction:
The Synuclein-One study is an ongoing NIH-funded 30-site multicenter trial of ~400 patients with synucleinopathies including pure autonomic failure (PAF), Parkinson's disease (PD), dementia with Lewy bodies (DLB), and multiple system atrophy (MSA). Enrollment will close in January 2023, with final data analysis in March 2023. PAF is a peripheral autonomic neurodegenerative disorder within the differential diagnosis of autonomic peripheral neuropathies. Over 5 years, approximately 10% of PAF patients phenoconvert to one of the central synucleinopathies. Objective: To describe the sensitivity, specificity, accuracy and precision of skin biopsy to detect the presence of intra-axonal phosphorylated alpha-synuclein in patients with synucleinopathies. This presentation will focus on PAF participants.

Methods:
After informed consent, all subjects complete structured neurologic examinations, disease history review, cognitive evaluation, orthostatic vital signs, RBD questionnaire, and an orthostatic hypotension questionnaire. Skin biopsies at the distal leg, distal thigh and posterior cervical region are acquired and processed at 2 independent laboratories with blinded quantitation of sensory and autonomic nerve fiber density and intra-axonal phosphorylated alpha-synuclein. Clinical diagnoses are confirmed by two independent clinicians who are blinded to pathological results.

Results:
Final unblinded results will be presented at the PNS 2023 annual meeting with specific details on sensitivity, specificity, accuracy and precision. In addition, synucleinopathy subgroup analysis will be performed to define unique pathological small fiber and autonomic characteristics of PAF and the central synucleinopathies, PD, MSA, and DLB.

Conclusions:
An unmet need exists for sensitive and specific tests in the differential diagnosis of the peripheral autonomic neuropathies. This is of particular importance for PAF given the potential for phenoconversion to a central neurodegenerative diseases that has important diagnostic, prognostic and therapeutic implications. The Synuclein-One study is the largest investigation of cutaneous phosphorylated alpha-synuclein detection across all four synucleinopathies and will advance neurodiagnostic testing in peripheral autonomic neurodegenerative disease.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: Supported by NIH grant R44 NS117214 (NINDS)

Keywords: Autonomic, Synuclein, PAF, Small fiber

Diagnostic evaluation of chronic polyneuropathies induced by oxaliplatin comparing Q-sweat to the current perception threshold and nerve conductions.

Poster No:
P 306

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Introduction:
Chemotherapy-induced peripheral neuropathy (CIPN) negatively affects the quality of life of many patients treated with oxaliplatin for breast cancer. Symptoms can persist long after treatment and often include neuropathic pain. We sought to characterize the neuropathies in terms of symptoms, neurological signs, and objective evidence of damage to the structure and function of the peripheral nerves. Furthermore, the diagnostic values of the Q-sweat test, current perception threshold (CPT), and nerve conduction studies (NCS) were compared.

Methods:
The severity of CIPN was evaluated in breast cancer patients treated with oxaliplatin-based chemotherapy. Sensory and motor symptoms were assessed using the neuropathy symptom scale (Korean version). A neurological examination was also performed. A nerve conduction study, current perception threshold (CPT), and Q-sweat test were performed. CIPN was assessed and the TNS-r score was calculated by a single examiner.

Results:
Patients complaining of neuropathy symptoms at least 3 months after the completion of oxaliplatin treatment (n = 30) were recruited. Clinically, only sensory functions were affected. Both sensory and motor fibers were affected in the NCS, showing, predominantly, signs of axonal damage. The NCS, Q-sweat, and CPT were abnormal in 20, 6 and 25 of the oxaliplatin-treated patients, respectively.

Conclusions:
Chemotherapy-induced peripheral neuropathy after oxaliplatin treatment is a sensory axonal neuropathy affecting only small nerve fibers in some patients. NCS is often normal; QST has a lower diagnostic sensitivity whereas CPT has a higher diagnostic sensitivity.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Current perception threshold, Chemotherapy induced neuropathy, Oxaliplatin

Macrophage Migration Inhibitory Factor (MIF): A Potential Therapeutic Target for Chemotherapy-Induced Peripheral Neuropathy

Poster No:
P 307

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Introduction:
Macrophage migration inhibitory factor (MIF) is an inflammatory cytokine expressed in immune cells and sensory neurons. The plasma levels of MIF increase after peripheral nerve injury and in painful conditions such as neuropathy, including diabetic neuropathy and Guillain- Barre Syndrome (GBS). Several studies demonstrated that MIF contributes to pain hypersensitivity and worsens neuropathy. However, no studies examined its role in chemotherapy-induced peripheral neuropathy (CIPN). Despite several decades of research, no effective therapies exist for CIPN. Therefore, this study examined the role of MIF in CIPN.

Methods:
We used a mouse model of Cisplatin-induced peripheral neuropathy (CisIPN) for this study, as Cisplatin is a leading neuropathy inducer in humans. ELISA was used to measure the plasma levels of MIF, and Von Frey Filament test was used to assess the mechanical sensitivity of the experimental animals. For MIF inhibition, the small molecule inhibitor CPSI-1306 was used.

Results:
We found that plasma levels of MIF increase remarkably in CisIPN models. We also found persistent expression of MIF in the sensory neurons of CisIPN animals. Further, we examined the effect of MIF inhibition on CisIPN development and severity. We found that concomitant administration of the MIF inhibitor CPSI-1306 along with Cisplatin effectively suppresses neuropathy, as evident from our mechanical hypersensitivity experiments using Von Frey Filaments. Our experiments showed similar results in both male and female CisIPN animals indicating that this approach is effective in both sexes.

Conclusions:
Overall, our study showed that MIF is a potential therapeutic target for CIPN, especially CisIPN.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: Establishment Grant, Saskatchewan Health Research Foundation (SHRF) College of Medicine Research Award (CoMRAD), College of Medicine, University of Saskatchewan.

Keywords: Chemotherapy-induced peripheral neuropathy, Cisplatin, Mechanical hypersensitivity, Macrophage migration inhibitory factor, CPSI-1306

Myotonic discharge and myoedema (mounding phenomenon) in acute phase of colchicine myopathy and neuropathy: Two-cases report.

Poster No:
P 308

Authors:
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Introduction:
Colchicine is a common and effective treatment for acute gout but can lead to severe acute myopathy and neuropathy due to its low toxicity and therapeutic thresholds. We present two cases with acute proximal weakness, paresthesias, allodynia, areflexia and myoedema (or mounding phenomenon) after treatment with colchicine.

Methods:
Our two cases were admitted to our department in 2020 and 2022 with the same manifestation. They are both females. After one week of exposure to colchicine, they presented acute proximal weakness, glove and stoking paresthesia, allodynia, and areflexia. Nerve conduction studies were normal, nEMG shows myotonic discharge and myopathic pattern in both of them. CK and muscle biopsy were normal in one patient. Myoedema was found when percussing on the anterior tibialis in the acute phase and disappeared after stopping colchicine for two weeks in two patients.

Results:
After two weeks of follow-up, both patients recovered their muscle strength to normal. Also, numbness and neuropathic pain remarkably decreased. The signs of myoedema also disappeared on the next visit. Neither patient had a repeated NCS or EMG.

Conclusions:
Myotonic discharge is a clinical sign reported in several studies of colchicine-induced myopathy and our two patients. Together with acute sensory neuropathy presentation, they reflect a temporary disorder of nerve and muscle membrane rather than an axonal loss or demyelinating, as NCS were normal in our two cases. Myoedema, or mounding phenomenon, which has also been described in malnutrition or hypothyroidism, is not mentioned in toxic myopathy. The phenomenon may be specific to acute colchicine myopathy and neuropathy, as colchicine was demonstrated to have an effect on the microtubule network and cell membrane function. Therefore, we suggest clinicians routinely check this sign when suspecting colchicine neuromuscular disorder, especially when the patient is on multiple medications.

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Yes

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References 4:
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Grant Support:

Keywords: Conchicine-induced myopathy and neuropathy, Myoedema, Mouding phenomenon, Myotonic discharge, Guillain-Barre syndrome different diagnosis

Autonomic nerve fiber involvement preclinical models of CIPN and in patients

Poster No:
P 309

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Introduction:
Chemotherapy-induced peripheral neuropathy (CIPN) is a common dose-limiting toxicity in the treatment of many cancers. Most CIPN studies preferentially focus on sensory fiber loss and dysfunction. Here, we compared the structural and functional recovery of autonomic fibers in sweat glands (SGNFD) and sensory fibers (IENFD) in mouse footpads after exposure to a maximum tolerated dose (MTD) of several common chemotherapy agents. Additionally, we assessed the recovery of peripheral sensory and autonomic fibers in skin biopsies of patients exposed to chemotherapy within 2 years, 2-5 years and 5+ years.

Methods:
Female Balb-c mice were treated with a MTD of four anti-tubulin drugs: paclitaxel (PCA,), ixabepilone (IXA,), eribuline (ERIB,), vinoelbine (VINO), or corresponding placebo given intravenously, MWF for two weeks. Recovery was assessed at 24-hours, 1, 2, 4, 8, 12 and 24 weeks following the last dose. Skin biopsies and footpads were processed to visualize nerve fibers using PGP9.5.

Results:
The recovery to baseline levels in Ixabepilone-treated mice occurred more quickly for IENFD (4-weeks) than SGNFD (8-weeks). In contrast, Vinorelbine and Eribuline treated mice showed SGNFD recovery was slower (24-weeks) compared to IENFD (4-weeks). PCA-treated animals showed more severe IENFD and SGNFD deficits compared to the other agents with both IENFD and SGNFD not recovering completely until 24-months. PCA-treated animals demonstrated reduced footpad sweat formation in a dunctional assessment of autonomic function. Among patients exposed to chemotherapy within 2 years, 2-5 years, 5+ years, sensory (IENFD) and autonomic (SGNFD) fibers were prominently affected compared to age/gender matched controls and though SGNFD approached normal control levels more slowly than IENFD.

Conclusions:
Together, these data indicate that autonomic nerve fibers are affected prominently in CIPN and suggest that autonomic dysfunction may be an important and under-appreciated sequela of chemotherapy exposure.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Chemotherapy neuropathy, small fiber neuropathy, sweat gland nerve fiber density, Intraepidermal Nerve Fiber Density

Neurofilament Light Protein as Early Biomarker of Chemotherapy-Induced Peripheral Neuropathy

Poster No:
P 310

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Institutions:
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Introduction:
Chemotherapy-induced peripheral neuropathy (CIPN) is a chronic, disabling, and potential painful condition seen in 60 % of cancer patients treated with adjuvant oxaliplatin. CIPN can have delayed onset and progress after concluded treatment. This indicates the need for an early biomarker, which can predict the risk of developing chronic CIPN and thereby assist the oncologist in tailoring treatment. Neurofilament light protein (NfL) is a structural protein found in nerve axons. Upon nerve damage NfL is released and detectable in blood. Its potential as a biomarker has been shown in other conditions with axonal degeneration. The aim of the study was to examine the effect of oxaliplatin on NfL levels both on cellular level invitro and in blood samples from patients receiving oxaliplatin to evaluate the potential of NfL as an early biomarker of CIPN.

Methods:
Human sensory neurons were developed from induced pluripotent stem cells and exposed to clinically relevant concentrations of oxaliplatin. Axonal damage was assessed using immunolabeling and high-content imaging. Following oxaliplatin exposure, the medium of the human sensory neurons was collected, and NFL levels were quantified using single-molecule array (SIMOA). Patients diagnosed with colorectal cancer undergoing chemotherapy treatment with or without oxaliplatin were included. Symptoms of CIPN was documented using two different scales (the TCNS or CTCAE score) and accumulative dosage and treatment regime was logged. Blood samples were taken; prior to, 3 months and 6 months after treatment start. NfL levels were analyzed using SIMOA.

Results:
In vitro oxaliplatin caused axonal damage to human sensory neurons in a concentration-dependent manner, and it correlated to NfL secretion from the neurons. In the clinical study, 20 patients treated with oxaliplatin and 10 without oxaliplatin were included and data-analysis is ongoing.

Conclusions:
Results from both setups will be presented at full at PNS annual meeting 2023.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: Novo Nordisk Foundation, Project Grants in Clinical and Translational Medicine 2020, NNF 20OC0065520, as part of Phd.

Keywords: Chemotherapy induced peripheral neuropathy, Neurofilament Light Protein, Biomarker, Cancer

Comparing Measures of Upper Limb Function for the Assessment of Chemotherapy-Induced Peripheral Neurotoxicity

Poster No:
P 311

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Introduction:
Upper-limb symptoms are often reported in the context of chemotherapy-induced peripheral neurotoxicity (CIPN), but objective quantification of deficits is often lacking. Stimulated-skin wrinkling (SSW) of the finger pulps has been previously utilised as a metric of small fibre dysfunction in other peripheral neuropathies. In this study, we examined and compared a range of neurophysiological and functional assessments of the upper-limb in the assessment of CIPN-severity.

Methods:
Participants were assessed cross-sectionally 3-to-24 months post-neurotoxic chemotherapy treatment (predominantly taxane or bortezomib). CIPN-severity was graded using a patient-reported outcome (EORTC-QLQ-CIPN20), a neurological examination score (Total Neuropathy Score-clinical version, TNSc), and a clinically-graded scale (NCI-CTCAE). Functional assessments on the dominant hand assessed sensory perception (Grating Orientation (GOT) task; Von-Frey monofilaments), and fine-motor skills (Grooved Pegboard). Nerve-conduction studies of the sensory and motor median nerve were undertaken. EMLA-cream was applied to distal digit tips of the non-dominant hand, and degree of skin wrinkling after 30 minutes was graded by two assessors and averaged. Associations between these measures and CIPN-severity were investigated using Spearman's or Pearson's correlations.

Results:
38 participants (mean age=59.6±12.1) with CIPN (NCI-CTCAE grade≥1) who were 14.0±8.6 months post-treatment completion were included. Eighteen participants (47%) reported upper-limb symptoms of CIPN. Reduced sensory perception via GOT was associated with higher CIPN-severity via patient-reported outcome ($r=0.4;p=0.01$) and higher neurological examination score ($r=0.4;p=0.007$). Higher GOT thresholds also associated with reduced sensory median amplitudes ($r=-0.5;p=0.006$), and reduced skin wrinkling scores ($r=-0.3;p=0.03$). Slower grooved pegboard time was associated with reduced sensory performance (GOT $r=0.6;p<0.001$, Von-Frey score $r=0.4;p=0.01$), and reduced skin wrinkling ($r=-0.4;p=0.01$). However, there were no associations between nerve-conduction studies or skin wrinkling and CIPN severity (all $p>0.05$).

Conclusions:
Although stimulated-skin wrinkling correlated with objective functional measures, it did not with patient-reported outcome measures of CIPN severity. More discriminating assessment tools are still needed to identify clinically relevant small-nerve fibre dysfunction.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Chemotherapy-Induced Peripheral Neurotoxicity (CIPN), Stimulated-Skin Wrinkling (SSW), EMLA, Outcome Measures , Functional Assessments

Single Center Experience of Carfilzomib-induced Peripheral Neuropathy

Poster No:
P 312

Authors:
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Introduction:
Proteosome inhibitors are a well-recognized cause of peripheral neuropathy. First-generation bortezomib carries the highest risk and is associated with a length-dependent painful sensory neuropathy. Second-generation proteosome inhibitors (carfilzomib, ixazomib) have an improved side effect profile. Previous studies report peripheral neuropathy incidence up to 13.9% with carfilzomib, compared to 30-60%. Little is known regarding the neuropathy phenotype and risk factors for development of neuropathy with carfilzomib.

Methods:
We searched our institution's Hematology database for multiple myeloma patients who received carfilzomib. Clinical information was reviewed to confirm onset of neuropathy with carfilzomib treatment. Clinical and electrophysiological findings were reviewed.

Results:
173 received carfilzomib at our institution, and 107 had pre-existing neuropathy prior to carfilzomib exposure. 27/173 patients (16%) developed new or worsening neuropathy. These patients were more likely to have diabetes mellitus and a family history of peripheral neuropathy. Frequency of neuropathy was similar in those who received carfilzomib monotherapy versus other regimens. Symptoms often began within the first 5 cycles (n=20, 74%) and were described as positive (n = 20, 74%); negative (n=24, 89%); painful (n=11, 41%). Weakness was uncommon (n=3, 11%). Neuropathy was a stocking-glove or stocking distribution. One patient developed a severe multifocal immune-mediated neuropathy. Pain was more common in those with pre-existing neuropathy. EMG demonstrated a length-dependent, sensorimotor axonal neuropathy. Neuropathy severity was moderate (grade 2, n=17, 63%) or severe (grade 3/4, n=10, 37%). Change or discontinuation of therapy was required in four patients, 2% of the total cohort.

Conclusions:
Carfilzomib causes a treatment-emergent length-dependent painful sensory neuropathy like bortezomib. The severity was often moderate to severe, but rarely led to treatment discontinuation. History of diabetes and family history of neuropathy were more common in patients who developed neuropathy. As with bortezomib, rare immune-mediated neuropathies can occur.

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Yes

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Grant Support:

Keywords: Treatment-induced neuropathy, Carfilzomib neuropathy, Proteosome inhibitor-related neuropathy, Toxic neuropathy, Chemotherapy neuropathy

Potential Role for Mesencephalic-Astrocyte Derived Neurotrophic Factor (MANF) in Peripheral Nerve Regeneration and Neuropathy

Poster No:
P 313

Authors:
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Introduction:
Mesencephalic astrocyte-derived neurotrophic factor (MANF) is a neurotrophic factor well studied for its protective roles in dopaminergic neurons in neurodegenerative conditions like Parkinson's Disease (PD). At the mechanistic level, MANF suppresses ER stress and unfolded protein response (UPR) to facilitate neuroprotection. It was also shown to activate the growth and survival-related PI3K/Akt and mTOR signaling in the central nervous system (CNS) neurons. However, MANF has not been studied much in the peripheral nervous system (PNS).

Methods:
Immunohistochemistry was performed to examine the distribution of MANF and Neuroplastin in the dorsal root ganglia (DRG) of healthy and axotomized (sciatic nerve transected) adult SD rats. Recombinant human MANF was used for supplementing MANF to in vitro primary sensory neuron cultures. The neurite outgrowth parameters were measured using the WIS- NeuroMath Software. ELISA was performed to measure plasma levels of MANF in the Cisplatin-induced peripheral neuropathy model in mice.

Results:
We found that MANF is expressed in a subpopulation of DRG neurons in male adult SD rats. A transection injury to the sciatic nerve slightly increased the expression of MANF in low-caliber sensory neurons, with no remarkable changes in its expression noted in satellite glial cells. Strikingly, the supplementation of MANF in adult rat primary sensory neuron cultures in vitro improved the neurite outgrowth parameters. We also found that its receptor Neuroplastin is expressed in sensory neurons and satellite glial cells. In the CIPN animals, we found a slight reduction in the plasma levels of MANF compared to the control animals, indicating that MANF-dependent neuroprotection may not be intrinsically active in CIPN.

Conclusions:
Overall, we found that MANF is expressed in the PNS and has the potential to improve peripheral nerve regeneration. Additional supplementation of MANF in nerve injury and neuropathy conditions may be therapeutic, but detailed studies are warranted to check this possibility.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: MANF , Peripheral Neuropathy, Nerve Regeneration, ER stress, Unfolded Protein Response

Structural investigation of SARM1, a protein that causes axon loss

Poster No:
P 314

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Introduction:
SARM1 is a pro-degenerative NADase that executes the programmed axon degeneration pathway, after nerve injury and in diseases including polyneuropathies and ALS. The ARM domain of SARM1 regulates its NADase activity; attenuating this activity delays axon degeneration, so SARM1 has become an important drug target. This project aims to characterise activation at the ARM domain allosteric site, where NMN and NAD bind in competition, respectively activating SARM1 and blocking its activation. In addition, this project is testing whether a rare, natural ARM domain mutant (SARM1W253C) in a patient with a complex disorder with motor and retinal symptoms, confers a gain-of-function consistent it having a causative role.

Methods:
Site-directed mutagenesis was used to modify the ARM domain allosteric site with artificial variants, or to introduce the SARM1W253C natural mutation. Variants were expressed in HEK cells to determine their influence on NAD levels and mutant proteins isolated using immunoprecipitation for NADase assays of basal and NMN-induced activity.

Results:
Several artificial mutants in the SARM1 ARM domain influence NAD levels in transfected HEK cells and alter basal and/or induced SARM1 NADase activity. Interesting patterns are emerging that will help understand how SARM1 becomes activated and potentially how to block activation therapeutically. Further characterisation of these residues is ongoing to understand more fully how they influence activation. The SARM1W253C natural variant was shown to decrease NAD levels in HEK cells to similarly low levels as one artificial variant. Purified SARM1W253C NADase assays are ongoing to determine whether it too is a constitutively active mutant, and how its activity compares to those reported previously in ALS.

Conclusions:
SARM1 ARM domain allosteric site residues regulate NADase activity, helping to understand how this site could be targeted to block activation. Initial data are consistent with SARM1W253C conferring gain-of-function, but recombinant protein assays are needed to confirm this.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: axon degeneration, SARM1, site-directed mutagenesis

Chronic SARM1 activation underlies NAD(P) loss in primary neurons expressing low levels of NMNAT2

Poster No:
P 315

Authors:
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Introduction:
The length, branching and high metabolic demand of axons makes them vulnerable to many stresses. Wallerian degeneration (or programmed axon death) is a well-characterised signaling pathway regulating axon survival and contributing to genetic, toxic and metabolic disease in animals and human disorders including ALS and other motor nerve disorders. The pathway is triggered when NMNAT2, an NAD-synthesising enzyme crucial for axon survival, is depleted. This activates SARM1, an NAD(P)-consuming enzyme that kills axons. Interestingly, acute or chronic NMNAT2 loss have distinct effects. In primary mouse neurons acute loss of a single Nmnat2 allele kills axons whereas chronic depletion of one allele is consistent with long-term axon survival. In vivo mice survive and remain healthy with an expression down to 30% of wild-type NMNAT2.

Methods:
Our study aims to understand whether chronic depletion of NMNAT2 can activate SARM1 in seemingly intact axons. We have used superior cervical ganglion (SCG) neurons from mice expressing 30% of normal NMNAT2 to study the effects on neurite outgrowth as well as NAD and NADP.

Results:
Neurons expressing low levels of NMNAT2 have neurite outgrowth defects and significantly less NAD and NADP than wild-type neurons. This loss of NAD and NADP is completely SARM1-dependent, suggesting that chronic activation of SARM1 leads to a constitutive depletion of these metabolites without causing axon degeneration. Additionally, application of the NAD precursor Nicotinamide Riboside (NR) does not boost NAD levels in SCG neurons from low-NMNAT2 expressing mice due to chronic SARM1 activation.

Conclusions:
A deficiency of NMNAT2 partially activates SARM1 even in axons that appear intact. It will be important to extend this to studies of other neuron types, including motor neurons, to establish what compensatory mechanisms are employed to allow axons with chronically active SARM1 to survive, and whether these indicate potential new therapeutic strategies for neurological disorders involving SARM1.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Axons, Degeneration, NMNAT2 , SARM1, NAD

RNA Sequencing Reveals Distinct Gene Expression Profiles In A Drosophila Model Of Chemotherapy-Induced Peripheral Neuropathy

Poster No:
P 316

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Introduction:
Many effective chemotherapy drugs are compromised by dose-limiting side effects that also affect long term quality of life. The platinum compounds, including cisplatin, cause lifelong painful toxic peripheral neuropathy (CIPN) during treatment for approximately 30% of patients. There are only a few known risk factors that reliably predict vulnerable patients. Existing treatments provide only symptomatic relief, and no curative or preventive treatments are in clinical use. Further research into and mechanisms of cellular resistance to cisplatin and risk factors, such as genetics, that influence patient susceptibility to CIPN is essential for improving treatment and quality of life for cancer survivors.

Methods:
We utilize Drosophila melanogaster as an in vivo genetic model of CIPN. Acute treatment with cisplatin causes climbing defects in a negative geotaxis assay, and cellular or biochemical assays reveal apoptotic neurons and cellular damage in the brain. We previously described a Drosophila strain (attP40) that is resistant to cisplatin neurotoxicity through a mechanism involving PGC1-α and Sirtuin-1. Sirtuin-1 activates many transcription factors, including PGC1-α. We hypothesized that altered gene expression profiles in neurons promote resistance to cisplatin in Drosophila. We performed RNA sequencing on brains of sensitive and resistant strains with and without cisplatin treatment. We performed differential expression and GO pathway analysis to assess gene expression profiles in each condition.

Results:
We observed distinct gene expression profiles between the two strains with and without cisplatin, including many genes predicted to be involved in the cisplatin response. Highly differentially expressed genes affect sensitivity to cisplatin. We also show our cisplatin-resistant strain uniquely upregulates genes and GO pathways involved with regulation of the cell cycle, DNA replication, and mitosis.

Conclusions:
Our results suggest that altered cell cycle regulation in the Drowse brain may affect sensitivity to cisplatin. This new genetic analysis has great potential to unveil novel mechanisms by which neurons protect themselves from cisplatin neurotoxicity.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Chemotherapy, Neuropathy, Drosophila, RNAseq

NonO Controls Axonal localization of Ribosomal Protein mRNA and Regulates Peripheral Axon Regeneration in Mice

Poster No:
P 318

Authors:
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Introduction:
During axon regeneration, axonal mRNA localization and local translation support robust axon regrowth. The RNA-binding protein NonO (p54nrb) is known as a central regulator of RNA nuclear export and has recently been implicated in motor function deficits and intellectual disability in humans. Here, we investigated the role of NonO as a regulator of axonal mRNA localization and axon regeneration after injury.

Methods:
Cultured mouse dorsal root ganglion (DRG) neurons were used as an in vitro model for analyzing axon regrowth and axonal RNA localization with lentiviral knockdown of Nono. Axotomy was given to the neurons to injure the axons and RNA or protein was separately collected from the cell body and axon areas. Axonal regeneration in vivo was assessed in mouse sciatic nerves by crushing the nerves with forceps and analyzing lengths of the regenerated axons immunolabeled for stathmin-2 at three days after crush. RNA-immunoprecipitation sequencing was performed by long-read sequencing of the immunoprecipitated RNA using anti-NonO or anti-inosine antibodies. De novo protein synthesis in axons was measured by a puromycin-labeling assay.

Results:
Axon regeneration was significantly improved by NonO-deficiency in cultures and in mice, demonstrating that NonO is a negative regulator of axon regeneration. In the NonO-binding RNA group identified by RNA-immunoprecipitation sequencing, we found that ribosomal subunit protein mRNA (RP-mRNA) were significantly enriched. Injury-induced axonal localization of the NonO-binding RP-mRNA was increased by knocking down NonO in cultured DRG neurons. Using puromycin assays, we show that axonal translation in injured neurons was increased by NonO-deficiency.

Conclusions:
Our data suggest that NonO controls axonal localization of RP-mRNA in injured neurons and that increased ribosomal protein expression at the axon tips may support local translation in injured axons, which promotes regeneration.

References:
No

References 1:

References 2:

References 3:

References 4:

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Keywords: NONO (p54 nuclear RNA-binding protein), axon regeneration, ribosomal protein mRNA, axonal translation, adenosine-to-inosine RNA editing

Exploiting HDAC6 specific inhibitors to reduce OHP-induced neurotoxicity

Poster No:
P 319

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Institutions:
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Introduction:
Histone deacetylases (HDACs) are a class of enzymes involved in the regulation of both histone and non-histone proteins [3]. Their action, regulation and involvement in various pathways, still not completely described, has puzzled the scientific community in recent years [2, 3, 4]. Currently, HDAC inhibitors (HDACi) are approved by the FDA for the treatment of malignancies [1]. Since the first HDACi had been discovered, others were developed to a total of 5 HDACi currently approved by FDA [1,3]. Besides the antineoplastic activity, recent findings pointed out also a possible neuroprotective effect for some HDACi [3]. Our research focuses on this double effect of HDACi, that could be exploited in combination with classical antineoplastic drugs, already known to induce CIPN (Chemotherapy-induced peripheral neuropathy), with the aim both to enhance the antineoplastic activity [3] and to reduce their neurotoxic side effect.

Methods:
Through the SRB assay, in the HT-29 cell line, the IC50 of 6 HDACi (SAHA, Belinostat, Romidepsin, SW-100, Ricolinostat, Panobinostat) and an antineoplastic drugs (oxaliplatin) was identified. The neurotoxic effect of both single and combination treatments was analyzed on Dorsal Root Ganglia (DRG) by the evaluation of their neurite length..

Results:
So far, our results demonstrated that, although not particularly effective in enhancing the antineoplastic activity, the combination of some HDACi and OHP resulted in reducing the neurotoxicity. In particular, HDACi targeting specifically HDAC6 (such as SW-100 and Romidepsin) resulted more effectively than pan-HDACi (SAHA and Belinostat) in their neuroprotective activity.

Conclusions:
Our findings could be useful to prove that the development of new and more specific HDACi are a possible key to enhance the antineoplastic effect while reducing the neurotoxicity.

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Keywords: Chemotherapy-induced peripheral neuropathy, HDACi, Neuroprotection, antineoplastic, HDAC

A Low-cost Wireless Body Area Network for Chemotherapy-induced Peripheral Neurotoxicity: Design and Preliminary Data

Poster No:
P 320

Authors:
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Introduction:
The diagnosis of chemotherapy-induced peripheral neurotoxicity (CIPN) is currently based on a clinician's impression of patient-reported symptoms, while objective assessment of peripheral nerve damage is less frequently used. As a result, CIPN is often detected later in the course of the disease. The use of wearables, sensors, and smart devices for early detection and monitoring of CIPN has been suggested but data are limited. In this context, wireless Body Area Networks (WBANs) are emerging for the implementation of health-care solutions for well-being, have been successfully applied to other neurological conditions and may be useful in CIPN

Methods:
To describe the architecture of a low-cost WBAN that can collect sensorimotor and autonomic data from the patients undergoing potentially neurotoxic drugs, and elaborate them to extract parameters, which can be used for early detection and monitoring of CIPN.

Results:
The WBAN is built upon accessible off-the-shelf wearable devices and an Android application and integrates up to eleven data collection nodes and sensors. It is derived from a WBAN previously applied to Parkinson's disease and stroke and characterized by low cost, extended battery life, and long transmission range. Data on the WBAN usability, wearability, accessibility, compliance, and persistence in 10 patients are reported, together with its early diagnostic value for CIPN.

Conclusions:
The WBAN might represent a useful smart device for detection and monitoring of CIPN and should be tested in larger populations.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: This research was partially supported by a Telemedicine 2021 Grant from the Brain Research Foundation Verona ONLUS Association to Stefano Tamburin and Graziano Pravadelli.

Keywords: Chemotherapy-induced peripheral neurotoxicity, Information and communication technology, Sensors, Telemedicine, Digital biomarkers

Clinical Characteristics of Patients with Sensory Ganglionopathy

Poster No:
P 321

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Introduction:
Sensory ganglionopathy is a rare form of neuropathy. The purpose of this study was to characterize patients with sensory ganglionopathy to describe their medical comorbidities, treatment and outcomes.

Methods:
The study was approved by our IRB. A retrospective review was performed for a five-year period, including charts containing the terms 'ganglionopathy' and 'neuronopathy.' Records were reviewed to include only patients with large fiber sensory ganglionopathy. The following information was obtained from medical records: demographics, clinical features, medical comorbidities, results of diagnostic testing, treatment, and clinical outcomes.

Results:
Twenty-nine patients were identified with large fiber sensory ganglionopathy. 76% were female, and 24% male. The mean age was 48 years. The most common medical conditions identified were alcohol abuse (11 patients, 38%) and vitamin deficiency (12 patients, 43%). Autoimmune condition was seen in 4 (definite) and 6 (possible) patients. Other conditions included paraneoplastic syndrome (2), genetic disorder (2), diabetes (3), chemotherapy (2), B6 toxicity (2), and idiopathic (4). Fifteen patients had cerebrospinal fluid results, with normal profile in nearly all. MRI showed abnormal signal in the spinal cord in 3 patients. Nerve biopsy showed severe axonal loss in 3 patients. Fourteen patients were treated with intravenous immunoglobulin (IVIG), eight with corticosteroids, two with plasma exchange, and four with rituximab. At most recent visit, 38% of patients were noted to have improvement, 59% stable symptoms, 3% worsened, and 3% deceased. While 24% of patients still required wheelchair, 33% were able to walk with a cane or without device.

Conclusions:
This retrospective study of sensory ganglionopathy found the most common comorbid conditions to be alcohol abuse and vitamin deficiency. Autoimmune conditions, genetic and paraneoplastic etiology were also seen. Many patients were treated with immunotherapy. Clinical improvement over time was seen in a third of patients.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: ganglionopathy, neuropathy, alcohol, inflammatory, paraneoplastic

Longitudinal comparative study of light-chain neurofilaments at development and recovery of chemotherapy-induced peripheral neurotoxicity

Poster No:
P 323

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Introduction:
The identification of a reliable predictive biomarker for the development and/or recovery of chemotherapy induced peripheral neurotoxicity (CIPN) remains an unmet need. Increasing evidence supports that light-chain neurofilament (NfL) could be a useful biomarker to quantify the extend of peripheral nerve damage due to chemotherapy. Preclinical models suggest variable change of NfL according to the type of agent and mechanism of neurotoxicity. The aim of the study is to ascertain differences in the evolution of plasma NfL (pNfL) levels among chemotherapies to better dissect the clinical usefulness of pNfL.

Methods:
This is a prospective longitudinal comparative study including three cohorts of patients treated with paclitaxel, brentuximab and oxaliplatin. All patients were assessed with the use of Total Neuropathy Score-clinical, Common Terminology Criteria for Adverse Events, EORTC QLQ-CIPN20 and nerve conduction studies (NCS) before, and periodically up to 12 months after finishing treatment. Serial pNfL levels were collected at the same timepoints and quantified using the highly-sensitive SIMOA technique. The changes in pNfL identified will be compared between groups of agents (platinum or microtubule disruptors) alone or in combination, and correlated with clinical and NCS data, depending on the degree of neuropathy and the grade of CIPN developed at finishing chemotherapy and at one year, to identify the usefulness of NfL as biomarkers of CIPN development and recovery, respectively.

Results:
61 patients are included, mostly women (65,5%). 24 patients received paclitaxel for breast cancer, 20 brentuximab for CD30+ neoplasms, and 17 oxaliplatin-based chemotherapy for gastrointestinal cancer. At finishing chemotherapy, 44,8%, 32,8% and 1,7% developed grade 1, 2 and 3, repectively. Analysis of pNfL levels is ongoing and will be reported as part of this abstract.

Conclusions:
Comparative analysis between agents with different mechanism of neurotoxicity are needed before implementing NfL as CIPN biomarker. pNfL might predict CIPN occurrence even in subclinical situation or predict the prognosis of CIPN long-term.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: This work was partially supported by a grant from Instituto de Salud Carlos III through the project PI20/00283 (Co-funded by European Regional Development Fund (ERDF)). We also thank CERCA Programme /Generalitat de Catalunya for institutional support.

Keywords: chemotherapy-induced peripheral neuropathy, peripheral neurotoxicity, biomarkers, neurofilaments

Solvent Abuse Neuropathy Mistaken for CIDP

Poster No:
P 324

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Introduction:
Solvent inhalation is a common form of substance abuse in youth especially in disadvantaged populations as glue and petrol are easy to obtain and relatively inexpensive. Solvent abuse is difficult to identify due to rapid toxin elimination. Unrecognised chronic solvent inhalation can lead to irreversible nerve damage. We describe a young male with a subacute motor predominant neuropathy diagnosed as solvent induced neuropathy on biopsy after poor response to initial treatment.

Methods:
A 21-year-old male presented to another institution with a 2-month history of progressive bilateral lower limb weakness and minor sensory loss on a background of alcohol abuse. Nerve conduction studies showed a sensorimotor neuropathy with slowed MNCVs. CSF analysis and MRI spine were unremarkable. A diagnosis of CIDP was made and an induction course of immunoglobulin (IVIg) was given with a plan for monthly IVIg infusions. A lack of improvement prompted a sural nerve biopsy.

Results:
Toluidine blue-stained nerve sections showed mild nerve fibre loss and the pathognomonic finding of frequent giant axons which were thinly myelinated or near naked. Teased fibre preparations confirmed frequent axonal swellings. The features resemble those seen in giant axonal neuropathy but in a 21-year old with a 2-month history that diagnosis was not tenable and solvent abuse was suspected. On obtaining further clinical history, petrol sniffing was confirmed.

Conclusions:
This case demonstrates the importance of thorough clinical history and adherence to electrophysiological and other diagnostic criteria in accurately diagnosing CIDP. Solvent abuse neuropathy is a rare CIDP 'mimic' but one where sural nerve biopsy is diagnostic. The nervous system is particularly susceptible to inhaled solvents due to its high lipid content. The neuropathy is characteristically motor predominant and reduced MNCVs are often reported. In the clinical setting of a subacute motor neuropathy, if solvent abuse is suspected, a sural nerve biopsy is useful given the pathognomonic histological findings.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Solvent Abuse Neuropathy , CIDP

Median nerve fascicular injury following COVID-19 vaccination

Poster No:
P 325

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Introduction:
Constriction neuropathy is a neurological disease characterized by fascicular constriction of peripheral nerve without any abnormality causing compression. The etiology of constriction neuropathy is still unclear. To the best of our knowledge, selective fascicular involvement of peripheral nerve following COVID-19 vaccination has not been reported. Herein, we report a case of constriction neuropathy of the median nerve fascicle following mRNA-1273 (Moderna) COVID-19 vaccination.

Methods:
A 42-year-old female visited the hospital with left thumb paralysis 3 days after administration of mRNA-1273 (Moderna) COVID-19 vaccine. She denied any history of recent trauma. She complained that she could not bend the thumb and that felt numbness and throbbing pain at left shoulder which radiated to anteromedial side of arm and distal part of forearm. The pain was prominent with wrist flexion during supination. Neurological examination revealed thumb flexion weakness of medical research council (MRC) grade 2, impairment of OK sign in her left hand, otherwise, other limbs were normal.

Results:
Blood analysis including leukocyte count, c-reactive protein, GM1 IgG antibody, IgG subclass, and complement (C3, C4) were normal. Serum interleukin-6 level was markedly elevated to 216.2pg/ml. In nerve conduction study (NCS) and needle electromyography (EMG), positive sharp waves and reduced recruitment was identified on flexor pollicis longus and first dorsal interosseous muscles. Magnetic resonance imaging (MRI) revealed constriction, swelling and torsion on proton density-weighted image and fat-suppression T2 weighted image at dorsomedial fascicle of the median nerve above the elbow joint. The ultrasonographic image showed incomplete constriction and swelling at the median nerve in the distal upper arm.

Conclusions:
Her symptoms were not improved with high-dose oral corticosteroid. Accordingly, interfascicular adhesiolysis and detorsion surgery is scheduled. We hypothesized that mRNA-1273 COVID-19 vaccine could induce the autoimmune cascade and focal inflammation and constriction of median nerve fascicle. Median nerve fascicular lesion should be considered wherein anterior interosseous nerve syndrome is suspected.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: COVID-19 vaccination, Median nerve, Fascicle, Injury

Inflammatory Neuropathy Consortium

Inflammatory Neuropathy Consortium (INC) Abstracts

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Serum Contactin-1 and neurofilament light as potential biomarkers of peripheral nerve injury in live myelinated sensory neuron cultures

Poster No:
P 326

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Introduction:
Serum neurofilament light chain (NfL) is reported to reflect axonal damage [1]. The axonal protein Contactin-1 (CNTN1) levels are significantly reduced in patients with paranodal antibodies [2], and may be a marker of paranodal pathology. We aim to further investigate the relationship of these proteins as fluid biomarkers to axonal and nodal/paranodal injury.

Methods:
We measured NfL and CNTN1 from the supernatant of a live co-culture system of stem cell-derived myelinated sensory neurons, treated with either healthy or nodal/paranodal- antibody-containing serum, using Luminex and Simoa platforms, respectively. Cultures were immunostained and imaged for injury.

Results:
At 24 hrs untreated co-cultures released low levels of NfL (mean 660 pg/ml) and CNTN1 (27pg/ml). NfL was undetectable in healthy serum alone, but if applied to cultures, supernatant NfL increased over time (1hr=926pg/ml 24hr=9109pg/ml) without visual evidence of axonal injury. After incubation with both anti-GQ1b-antibody-containing serum (positive control for complement-mediated axonal injury) and healthy serum (source of complement), NfL levels increased 10-27 fold (1hr=25000pg/ml, 24hr=96,393pm/ml), strongly correlating with axonal fragmentation. After incubation with nodal/paranodal-antibody-positive serum, with or without healthy serum, NfL increased only after 24hrs (range 2174-14351pg/ml). Axonal injury correlated less markedly. In contrast, CNTN1 levels were raised in healthy serum (mean 2703 pg/ml), and this was static in cultures treated with healthy serum. Supernatant CNTN1 levels of cultures treated with antibody-containing serum (GQ1b or nodal/paranodal) increased only in the presence of healthy serum, remaining static between 1 and 24hrs, despite imaging evidence of axonal fragmentation.

Conclusions:
These preliminary data strengthen the concept that NfL levels acts as a fluid biomarker of axonal injury. For CNTN1 protein, it could not be demonstrated that decreased levels are related to neuronal injury, at least in the current set-up. Using this live model provides a unique opportunity to study biomarkers as dynamic and translatable endpoints in in-vitro studies.

References:
Yes

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References 3:

References 4:

Grant Support: GBS|CIDP Foundation International Benson Fellowship awarded to JF (1709HM001/SB17) and a Medical Research Council UK Clinician Scientist Fellowship (MR/P008399/1) awarded to SR

Keywords: Contactin-1 protein , Neurofilament light chain, Human induced pluripotent stem cell-derived sensory neurons, Nodal/paranodal antibodies

Efficacy and Safety of Nipocalimab for Adults with Chronic Inflammatory Demyelinating Polyneuropathy: The ARISE Study

Poster No:
P 327

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Introduction:
Chronic inflammatory demyelinating polyneuropathy (CIDP) is a rare, chronic autoimmune disease of the peripheral nervous system characterized by progressive weakness and impaired sensation. Nipocalimab is a fully human aglycosylated immunoglobulin (Ig)G1 monoclonal antibody designed to selectively bind, saturate, and block the IgG binding site on the endogenous neonatal Fc receptor. Nipocalimab is administered via intravenous infusion. The ARISE study (NCT05327114) is a Phase 2/3 multicenter, double-blind, placebo-controlled, parallel-group, randomized withdrawal study evaluating the efficacy and safety of nipocalimab in adults with CIDP.

Methods:
The study consists of the following periods: (1) Screening (≤4 weeks)/Run-in (≤12 weeks), which includes identification of patients with active CIDP; (2) Stage A (open-label, 12 weeks), with participants receiving nipocalimab loading dose, then once every 2 weeks (q2w); (3) Stage B (double-blind, placebo-controlled, ≤52 weeks), with participants randomized 1:1 to nipocalimab q2w versus placebo; (4) open-label extension (variable duration), with participants receiving nipocalimab q2w. Key inclusion criteria include adults ≥18 years with CIDP, progressing/relapsing forms, confirmed by independent adjudication committee; CIDP disease activity score ≥3; and adjusted Inflammatory Neuropathy Cause and Treatment disability score 2–9. Patients with pure sensory CIDP or chronic immune sensory polyradiculopathy (CISP), or other diagnoses that could better explain their clinical presentation are excluded. Primary endpoint: time-to-first occurrence of a relapse event in Stage B. Secondary efficacy endpoints: time to initial response to nipocalimab and percentage of nipocalimab responders in Stage A, and change from baseline in functional measures (e.g., grip strength, MRC sum score, etc.) in Stage B. Other secondary endpoints: safety/tolerability, pharmacokinetics, immunogenicity, and pharmacodynamics of nipocalimab.

Results:
The study is currently enrolling patients, targeting approximately 300 patients, with primary study completion date anticipated in 2026.

Conclusions:
This ongoing Phase 2/3 study will assess the efficacy, safety, pharmacokinetics, and pharmacodynamics of nipocalimab in adults with CIDP.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: Janssen Research & Development, LLC

Keywords: Chronic inflammatory demyelinating polyneuropathy, Autoimmune disease

The Effect of Dimethyl Fumarate on Chronic Experimental Autoimmune Neuritis in Lewis Rats

Poster No:
P 328

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Introduction:
Experimental autoimmune neuritis (EAN) is an animal model for the human immune-mediated neuropathy. Immunomodulatory agent, dimethyl fumarate (DMF) is widely used for a disease modifying therapy of multiple sclerosis, however, its effect on chronic form of peripheral neuritis remains obscure. The objective of this study was to elucidate the effect of DMF on EAN.

Methods:
Female Lewis rats were immunized with thiopalmitoylated synthetic peptides of P0 protein to induce chronic EAN. After immunization, DMF (200mg/kg) or vehicle was given by oral gavage daily. At 16 days pot-immunization (dpi), cauda equina (CE) were removed from five rats from each group, served for RNA extraction and histological examination. Semi-quantitative real time PCR were performed for comparing interferon gamma (IFN) and IL-10 messages. From 16 dpi, eight rats in control group were randomly selected to be treated with DMF (Delay). At 32 dpi, all rats were euthanatized and CE were removed, examined as above.

Results:
All vehicle rats developed weakness of tail by 12 dpi followed by ascending flaccid paralysis that peaked at 17~19 dpi. DMF group were significantly mild from 14 to 24 dpi ($p < 0.05$ by Mann-Whitney U-test). Delay group became milder than control group from two days after DMF initiation although statistically not significant. In active stage (16 dpi), DMF group showed strong suppression of IFN expression compared to vehicle group ($p < 0.05$) with reciprocal up-regulation of IL-10 expression (not significant). During recovery stage in vehicle and Delay groups, IFN and IL-10 expression remained high level despite paralysis already recovered.

Conclusions:
DMF can ameliorate EAN via suppression of pro-inflammatory cytokines with anti-inflammatory cytokine activation. The difference in IFN and IL-10 expression compared to acute EAN model may reflect chronicity of the current model. Further investigation is needed to prove therapeutical significance of this treatment in inflammatory neuropathy.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: dimethyl fumarate, experimental autoimmune neuritis, interferon gamma

The Evaluation of Efficacy and Safety of Additional Rituximab in Refractory CIDP Patients With IgG4 Autoantibodies by Patient Requested Medical Care

Poster No:
P 329

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Introduction:
To evaluate the efficacy and safety of rituximab for the treatment of treatment-resistant CIDP in IgG4 subclass autoantibody-positive patients in a Patient Requested Medical Care (JRCTs041210046) that followed the relevant POC clinical study (RECIPE study: NCT03864185).

Methods:
Five patients who had previously been shown to be positive for IgG4 anti-NF155 antibodies and who had received intravenous rituximab or placebo for the treatment of CIDP were included. During the period, existing treatments such as corticosteroids and IVIg could be continued, while no new treatment that could affect the disease course of CIDP could be started or the dose increased from the existing dose. Endpoints included adjusted INCAT Disability Scale, grip strength on the Martin vigorimeter, and Rasch-Built overall disability scale (R-ODS), MRC Sum Score, nerve conduction test findings, CSF protein concentration, and others.

Results:
The first patient was enrolled in June 2021, five patients were enrolled in November 2021, and all five patients were evaluated at 52 weeks in November 2022. 4 of the 5 patients showed at least 1 point improvement on the INCAT scale and improvement in grip strength, R-ODS, and MRC Sum Score. The patients were evaluated in the RECIPE study. This included a placebo-treated patient in the RECIPE study who did not improve on the INCAT scale, who also improved after receiving rituximab. One patient who did not improve at the 52-week evaluation had an ankle fracture due to a fall during the evaluation, but this was not considered to be related to the rituximab treatment. No other safety issues were identified for the continuation of the study.

Conclusions:
Following the RECIPE study, the efficacy and safety of rituximab in anti-NF155 IgG4 antibody-positive patients with a clinical presentation of refractory CIDP were confirmed.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: AMED (JP20lk0201080)

Keywords: chronic inflammatory demyelinating polyneuropathy, rituximab , NF155 IgG4, nodepathy, Patient Requested Medical Care

Schwann Cells Contribute to the Inflammatory Response of Sural Nerves in Patients with Polyneuropathies

Poster No:
P 330

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Introduction:
Polyneuropathy (PNP) is associated with pain in 50 % of the cases independent of the etiology. Inflammatory mediators can modulate nerve degeneration, regeneration and pain. Peripheral nerve fibers are accompanied and supported by Schwann cells, which might get activated upon stimuli and contribute to a pro-inflammatory environment leading to pain. In this study, we aim to elucidate the role of Schwann cells in the inflammatory environment taking place at the peripheral nerves of patients with PNP. We investigated the response of sural nerve fascicles and Schwann cells, isolated from patients with PNP, upon pro- and anti-inflammatory stimuli.

Methods:
PNP patients were recruited and as part of their diagnostic work-up, sural nerve biopsies were collected, and Schwann cells were isolated. Sural nerve fascicles and Schwann cells were stimulated with pro-inflammatory stimuli [lipopolysaccharide (LPS)] and samples were collected at defined time points. Pro- and anti-inflammatory markers were analyzed through RT-qPCR and new generation ELISAs (ELLATM). Axonal injury to nerve fascicles upon stimuli was assessed by the release of neurofilament light-chain (NFL).

Results:
We found a higher gene expression and increased release of interleukin (IL) 6, IL-8 and the CC-chemokine ligand 2 (CCL2) by nerve fascicles and Schwann cells upon treatment with LPS. Different levels of NFL were also detected released by the nerve fascicles. Resveratrol was able to reduce the cytokine release in Schwann cells. Furthermore, we demonstrated a patient-inherent inflammatory response in Schwann cells and nerve fascicles.

Conclusions:
This study provides insight in the inflammatory response patterns of human Schwann cells and sural nerve fascicles upon in vitro pro- and anti-inflammatory stimulation. Moreover, our results describe the potential pro-inflammatory role of Schwann cells in sural nerve inflammation and postulate patient-inherent inflammatory environments.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: European Union’s Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie Grant Agreement No. 764860

Keywords: Schwann cell, Inflammation, Cytokines, Nerve fascicle, Polyneuropathy

Characteristics of SFN Patients with THD or FGFR3 Antibodies: A Single Center Retrospective Study

Poster No:
P 331

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Introduction:
Antibodies to trisulfated heparin disaccharide (TS-HDS) and fibroblast growth factor receptor 3 (FGFR-3) have been recently reported in small fiber neuropathy (SFN) cases. Therefore, we aimed to describe clinical features in such patients and make a comparison with seronegative cases.

Methods:
We retrospectively evaluated both groups' demographic characteristics, clinical presentation, comorbidities, laboratory, biopsy, and electrophysiologic findings. We used the chi-square test for categorical and t-test for continuous variables.

Results:
In our cohort of 109 patients, positive autoantibodies were detected in 46 of them. Forty-one patients (37.7%) tested positive for either TS-HDS or FGFR-3. In our cohort, 87.8% were women, 82.9% were white, and the median age at diagnosis was 49.1 years. Of the seropositive group, 68.3% had non-length-dependent symptoms, and 85.4 % presented with chronic symptoms. The most common presenting symptoms were paresthesia/pain (97.6%) and numbness (82.9%). Psychiatric diseases (53.7%), fibromyalgia (43.9%), and migraine (36.7%) were the most commonly reported comorbidities. Diabetes mellitus was reported in 12.2% of the patients. Nerve conduction studies/EMG demonstrated the sural nerve's decreased nerve sensory action potential in 6 patients (14.6%). In addition, reduced epidermal nerve fiber density (ENFD) on skin biopsy was found in 60.6% of the patients. Statistical analysis between these two groups was significant only for a higher rate of normal or low-normal skin biopsy results in the seropositive group (28.6% vs. 7.9%, p - 0.009).

Conclusions:
We showed the presence of these novel antibodies in almost a little more than one-third of the cases. In addition, our study showed a higher rate of normal or low-normal skin biopsy in the seropositive group. This finding increases the significance of autoantibody studies in SFN patients with normal/low-normal skin biopsy.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: None

Keywords: Small Fiber Neuropathy, Antibodies, FGFR3, Trisulfated Heparin Disaccharide

Evaluation Of A Sensor-Equipped Glove In The Follow-Up Of Patients With Chronic Immune-Mediated Neuropathies

Poster No:
P 332

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Introduction:
Patients with chronic immune-mediated neuropathies such as multifocal motor neuropathy (MMN) or chronic inflammatory demyelinating polyneuropathy (CIDP) on therapy with intravenous immunoglobulins (IVIg) require periodic and standardized examinations to individually titrate the treatment based on disease activity. However, current tools often lack functional relevance, sensitivity to detect small changes of neurological deficits or are not feasible enough. Therefore, the treatment decision still often relies in parts on the subjective judgement of the patient. Here, we evaluated a sensor-equipped glove to monitor motor hand function in the surveillance of patients with chronic immune-mediated neuropathies in comparison to established tools.

Methods:
34 patients with chronic immune-mediated neuropathies (i.e., MMN or CIDP) were enrolled in a prospective trial. Examinations were performed at five time points, depending on the individual intervals of IVIg therapy. At each timepoint MRC Sum Score, INCAT Disability Score, INCAT Sensory Sum Score, I-RODS as well as grip strength analyses (vigorimeter and dynamometer) were performed. Moreover electrophysiological and nerve ultrasound examinations were analyzed twice. Furthermore, patients conducted defined exercises with the sensor-equipped glove in a gamified computer environment to assess different aspects of motor hand function.

Results:
We found a good test-retest reliability of the exercises performed with the glove. Furthermore, the glove was able to sensitively identify individuals with impaired hand function relevant to daily life within the cohort and moreover showed good specificity in this regard. Correlations of the performance assessed by the glove with a set of diagnostic standard tools in the individual course of disease were revealed.

Conclusions:
The sensor-equipped glove evaluated in this study holds great promise as an additional follow-up tool for patients with chronic immune-mediated neuropathies and for neurological diseases in general, especially if motor hand function is affected. Technical caveats revealed by our study will help to improve such innovative diagnostic tools and to find suitable study designs for further trials.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: chronic immune-mediated neuropathies, outcome measures, sensor-equipped glove, intravenous immunoglobulins, motor hand function

Prospective Study Of Electrophysiological Data Associated With The Prognosis Of Guillain-Barre Syndromes (GBS)

Poster No:
P 333

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Introduction:
The functional prognosis of Guillain-Barré syndromes (GBS) is uncertain. It is essential to identify at diagnosis the forms with a poor outcome. Our objective is to determine in a prospective study the initial electrodiagnostic (EDX) data associated with the functional prognosis of GBS.

Methods:
GBS meeting the Brighton diagnostic criteria, who had a systematized EDX protocol within 21 days of the onset of symptoms (sensory and motor nerve conductions of the median, ulnar, fibular, and tibial nerves; blink reflex; H-reflex on the tibial nerves; and facial nerve) were included. A poor prognosis was defined by a Guillain-Barré disability score greater than 2 (walking without assistance) at 3 months of follow-up.

Results:
41 patients were included in the study. No significant difference was observed for criteria of age, sex and length of hospital stay between the 2 groups. A diagnosis of 'classic' Guillain-Barre syndrome was made in 30 (73.1%) of patients; 4 (9,8%) were AMAN syndromes and 2 (4.8%) were Miller-Fischer syndromes. The sum of compound muscle action potential of the eight tested motor nerves was significantly lower in the poor outcome group comparatively to the good outcome group (p= 0,03). The mean number of nerves with absent or distant F waves was 2.45 in the good outcome group and 5.38 in the poor outcome group (p=0,03). The mean number of nerves with conduction blocks was 1.67 in the good prognosis group and 2.45 in the poor outcome group (p=0,01)

Conclusions:
An ENMG, even when performed at an early stage of Guillain-Barré syndrome, could help predict patients with a poor outcome. To our knowledge, this is the first prospective electrophysiological study focusing on functional prognosis of GBS

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: acute polyradiculopathy, ENMG , poor outcome, prospective cohort

IgM Peripheral Neuropathy Rasch-built Overall Disability Scale (IgM-PNP-RODS): A Patient-Reported Outcome Measure by The IMAGiNe Study

Poster No:
P 334

Authors:
Tatiana Hamadeh[1], Perry Van Doormaal[2], Johannes van de Mortel[2], DAVID CORNBLATH[3], Alexander Vrancken[2], Nicolette Notermans[4], Catharina Faber[1], Ingemar Merkies[5], on behalf of the IMAGiNe study consortium[6]

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Introduction:
The IMAGiNe consortium presents the results of the first study aim: the construction of an IgM peripheral neuropathy (IgM PNP)-specific patient-reported outcome measure at the level of activity and participation. IgM ±anti-MAG peripheral neuropathy is a rare and slowly progressive disorder associated with increasing rates of disability (1). A standardized interval measure to adequately capture limitations is urgently needed to support study designs and bring us closer to positive clinical trial results (2). Therefore, an international observational prospective cohort study was initiated; the IMAGiNe (IgM ± Anti-Myelin Associated Glycoprotein [MAG] peripheral Neuropathy) study.

Methods:
After 7 years of data collection and based on a well-defined cohort of over 250 participants from 8 different countries, the IgM-PNP-RODS (Rasch-built Overall Disability Scale) will be constructed using the Rasch analysis and fulfilling classic and modern clinimetric requirements. The systematic approach for analysis of model fit, response category ordering, item bias, and local response dependency will be described to justify the items remaining. Internal consistency and test-retest validity will be evaluated using entry scores and the T1 assessments performed after 2-4 weeks of inclusion. Construct and heuristic validity will be analyzed using additional parameters of the IMAGiNe study - including among others; the EuroQol Quality of Life EQ-5D questionnaire scores and Patient Global Impression of Change (PGIC). Furthermore, the diversity of the cohort will allow for a cautious assessment of cultural bias and the achievement of cross-cultural validity.

Results:
The IgM-PNP-RODS will be a functional interval measure suitable for parametric statistics and practical for clinical use. Ultimately, its development will help the research community overcome previous barriers associated with the use of inconsistent suboptimal ordinal measurement tools (3).

Conclusions:
Starting with the construction of proper scales for accurate assessment and follow-up, the upcoming IMAGiNe study results will provide large cohort observations needed for evidence-based practice and consensus.

References:
Yes

References 1:
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References 2:
(2) Vanhoutte EK, Faber CG, Merkies IS. 196th ENMC international workshop: Outcome measures in inflammatory peripheral neuropathies 8-10 February 2013, Naarden, The Netherlands. Neuromuscul Disord 2013;23(11):924-33.

References 3:
(3) Lunn MP, Nobile-Orazio E. Immunotherapy for IgM anti-myelin-associated glycoprotein paraprotein-associated peripheral neuropathies. Cochrane Database Syst Rev 2016;10(10):CD002827.

References 4:

Grant Support: (1) 2015 GBS CIDP Foundation International Mazawey Fellowship. (2) The Foundation for Peripheral Neuropathy. Partial funding for recruitment of subjects in international participating institutions (Our institutions, the coordinating centers in the Netherl

Keywords: IgM antiMAG Peripheral neuropathy, Monoclonal gammopathy of undetermined significance (MGUSP), Patient-reported outcome measures, Paraproteinemic neuropathy, Clinimetrics

Patient-reported Health-related Quality of Life in Guillain–Barré Syndrome: A Prospective Cohort Study Using EQ-5D-5L

Poster No:
P 335

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Introduction:
Guillain–Barré Syndrome (GBS) is an acute immune-mediated polyradiculoneuropathy with several chronic sequalae including restricted mobility, self-care, fatigue and depression. However, health-related quality of life (HRQoL) data in GBS is still scarce. The study aimed to compare the HRQoL in GBS patients who received specific or supportive treatments.

Methods:
We included 114 patients with GBS in Bangladesh who were enrolled from 2013 to 2016 and who completed follow-up of all studied time-points at 1-month (baseline), 1-year, 2-year and 3-year. HRQoL was measured by EQ-5D-5L and visual analogue scale (VAS). Descriptive analyses and independent-T-test were done to compare HRQoL among GBS patients who received specific or supportive treatment.

Results:
Among 114 patients with GBS, 66% (n=75) were male with a median age of 30 years (IQR 19,47). Majority (66%) of the patients were bedridden (GBS disability score 4) during enrollment. Twenty-one (18%) patients required mechanical ventilation. Two-thirds (69%, n=79) of the patients did not receive any specific treatment. Intravenous immunoglobulin (IVIg) and plasma exchange (PE) were given to 8% and 23% patients respectively. The mean(±SD) of EQ-5D-5L-indices of the patients who received specific treatments or supportive care were 0.116±0.371, 0.197±0.398, p=0.299 at base line (1-month); 0.719±0.238, 0.779±0.234, p=0.219 at 1-year; 0.782±228, 0.842±223, p=0.197 at 2-year; 0.851±0.201, 0.875±0.213, p=0.569 at 3-year respectively. Similarly, the mean EQ-VAS scores were not statistically significant between patients who received or did not receive specific treatment. In each EQ-5D-5L dimension, the proportion patient receiving specific or supportive treatment were comparable during all studied time-points.

Conclusions:
HRQoL was similar at all studied time-points in GBS patients who received or did not receive specific treatment. Further, controlled studies are required to evaluate HRQoL in larger GBS cohorts. This study reinforces the need of a better treatment option and the importance of patient-reported outcome for management of GBS.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Guillain–Barré syndrome, Patient-reported outcome, GBS, HRQoL, EQ-5D-5L

Cerebrospinal Fluid Adenosine Triphosphate And Clinical Features In Patients With Chronic Inflammatory Demyelinating Polyradiculoneuropathy

Poster No:
P 336

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Introduction:
Adenosine triphosphate (ATP) is involved in the regeneration of peripheral nerves, and neuron-derived ATP is thought to act as an alarm messenger for Schwann cells. Serum neurofilament light chain (sNfL) is recognized as a biomarker reflecting the disease activity of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). Because there have been no reports examining the correlation between cerebrospinal fluid (CSF) ATP and sNfL in CIDP, we investigated to elucidate the clinical significance of CSF ATP in patients with CIDP.

Methods:
Six patients with CIDP and 16 with idiopathic normal pressure hydrocephalus (iNPH) were enrolled in this study. CSF ATP and sNfL were assayed before treatment and/or at relapse in patients with CIDP. CSF ATP was measured by luciferase luminescence method. We investigated the correlation between CSF ATP, sNfL and clinical characteristics.

Results:
The levels of CSF ATP were significantly higher in patients with CIDP than those in iNPH ($p=0.0025$). The levels of sNfL decreased during the maintenance treatment with IVIg in CIDP patients, suggesting that axonal damage was ameliorated by the maintenance treatment. There was a negative correlation between CSF ATP and sNfL in patients with CIDP ($\rho=-0.943$, $p=0.0048$). Tibial nerve conduction velocity showed a positive correlation with the levels of CSF ATP, while it showed a negative correlation with sNfL.

Conclusions:
The levels of CSF ATP are significantly increased in patients with CIDP, and inversely correlated to those of sNfL. CSF ATP may be a potential biomarker reflecting intactness of CIDP.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: adenosine triphosphate, neurofilament light chain, CIDP, biomarker

CIDP Mimics study: improving the accuracy of the diagnostic process in CIDP

Poster No:
P 337

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Introduction:
Misdiagnosis of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is common, resulting in ineffective treatment, and preventable secondary axonal damage. Accurately diagnosing CIDP is important to improve long-term disease outcome in patients. The aim of the CIDP mimics study is to identify factors that can differentiate CIDP from its mimics early in the diagnostic process.

Methods:
This is a prospective observational multicenter cohort study conducted in the Netherlands. Patients are eligible if they are aged 18 years or older, and CIDP is included in the differential diagnosis after first contact at the (outpatient) clinic. We aim to include at least 200 patients. After obtaining informed consent, medical history, and results of neurological examinations and tests (such as EMG) are collected. Patients will not undergo additional testing for the purpose of this study, but residual biomaterials will be collected. The diagnosis registered in the patient file at entry, 3, and 6 months after inclusion will be evaluated.

Results:
By January 1st 2023, 28 patients have been included in the study. Of these patients, 58% are male, with ages ranging from 23 to 82 years at inclusion. The initial differential diagnosis varies, including neuropathies of other etiology, systemic disorders such as vasculitis, and hematological malignancies. Of the 12 patients with three months follow-up, two have been diagnosed with CIDP. At six months follow-up, three out of ten patients are diagnosed with CIDP.

Conclusions:
As there is no gold standard, the results of the CIDP mimics study may improve the diagnostic process in CIDP. An update of the preliminary results of the CIDP mimics study will be reported at the upcoming annual PNS meeting. We welcome collaborations with new centers.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: CIDP, CIDP mimics, Diagnostic accuracy

The International CIDP Outcome Study (ICOS): An Update

Poster No:
P 338

Authors:
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Introduction:
Chronic inflammatory demyelinating polyneuropathy (CIDP) is a rare immune-mediated polyneuropathy. Heterogeneity in both clinical presentation and electrodiagnostic features complicates the diagnosis, especially in CIDP variants. The International CIDP Outcome Study (ICOS) aims to improve the description of CIDP, CIDP variants, and their characteristics to enhance future therapeutic considerations and prediction of long-term outcome in patients.

Methods:
ICOS is a prospective, observational, multicenter study in which three Dutch university CIDP expert centers collaborate.[1] Patients fulfilling the EFNS/PNS 2010 criteria for CIDP are eligible to participate.[2] Clinical, diagnostic and treatment data are collected, as well as biomaterials (DNA, cerebrospinal fluid, and serial serum samples). For the first two years, follow-up visits are scheduled every 6 months, and then annually thereafter. Validated disability scales and patient reported outcomes, such as RODS, R-FSS, and EQ-5D-5L, are assessed at each visit.

Results:
By 1st of January, 2023, a total of 300 patients are enrolled (63% men, median age at diagnosis of 59 years). Acute-onset CIDP (nadir within 8 weeks from disease onset) is reported in 30% of patients. At study entry, 71% of patients are diagnosed with typical CIDP, whilst 28% of patients have a variant of CIDP (asymmetric 15%, predominant motor 6%, -sensory 3% or predominant distal involvement 4%). At study entry, 44% of patients treated with IVIg reported end of dose symptoms, which decreased to 23% at 12 months and 14% at the 24 month follow-up.

Conclusions:
ICOS aims to optimize the diagnostic process and treatment strategies for CIDP, in order to improve long-term outcome. The decrease in end of dose symptoms in patients treated with IVIg during follow-up might result from dose adjustments or stabilization of disease symptoms. Further harmonization of study protocols will allow close collaboration of ICOS with other registries, such as IncBase.

References:
Yes

References 1:

Bunschoten C, Eftimov F, van der Pol WL et al. International chronic inflammatory demyelinating polyneuropathy outcome study (ICOS): Protocol of a prospective observational cohort study on clinical and biological predictors of disease course and outcome.

References 2:
Van den Bergh PY, Hadden RD, Bouche P et al. European Federation of Neurological Societies/Peripheral Nerve Society guideline on management of chronic inflammatory demyelinating polyradiculoneuropathy: report of a joint task force of the European Federati

References 3:

References 4:

Grant Support:

Keywords: CIDP, long-term outcome, end of dose

Anti-myelin-associated-glycoprotein antibodies in patients diagnosed with chronic inflammatory demyelinating polyneuropathy

Poster No:
P 339

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Introduction:
Previous studies reported antibodies against myelin-associated-glycoprotein (MAG) in some patients diagnosed with chronic inflammatory demyelinating polyneuropathy (CIDP) without IgM-monoclonal gammopathy. The clinical relevance of these findings is debated. In this study, we aim to investigate the presence and titer course of anti-MAG antibodies in a large cohort of Dutch CIDP patients, in relation to clinical and diagnostic features.

Methods:
In the International CIDP Outcome Study (ICOS), patients diagnosed with CIDP according to the EFNS/PNS 2010 diagnostic criteria are included.[1,2] For each patient, we tested the sample taken closest to the time of CIDP diagnosis for anti-MAG antibodies using ELISA. In routine diagnostic testing, a test result of >10000 Bühlmann Titre Units (BTU) is considered positive, while the EAN/PNS 2021 Guideline for CIDP recommends 7000 BTU as threshold.[3] Since the clinical relevance of test results between 1000-10000 BTU is debated, we tested follow-up samples if the first sample test result was above 1000 BTU.

Results:
For the 235 included patients, 11 samples (4.6%) were tested above the threshold of 1000 BTU for anti-MAG antibodies. Five of these patients had typical CIDP whereas six had a CIDP variant. Two of 10 patients with a test result between 1000 and 10000 BTU had a known IgM-monoclonal gammopathy, and routine anti-MAG antibody testing at time of diagnosis was negative. Only one patient tested above the threshold of 7000 BTU (56514 BTU). This patient fulfilled the criteria for typical CIDP and did not have an IgM-monoclonal gammopathy. Furthermore nerve conduction studies and treatment response were compatible with CIDP.

Conclusions:
None of the patients with a known IgM gammopathy, and only one patient without a IgM-monoclonal gammopathy, tested above the threshold of 7000 BTU for anti-MAG antibodies recommended in the EAN/PNS 2021 Guideline. Further clinical details and serial titer values, will be presented at the PNS Annual Meeting.

References:
Yes

References 1:
Bunschoten C, Eftimov F, van der Pol WL et al. International chronic inflammatory demyelinating polyneuropathy outcome study (ICOS): Protocol of a prospective observational cohort study on clinical and biological predictors of disease course and outcome.

References 2:
Van den Bergh PY, Hadden RD, Bouche P et al. European Federation of Neurological Societies/Peripheral Nerve Society guideline on management of chronic inflammatory demyelinating polyradiculoneuropathy: report of a joint task force of the European Federati

References 3:
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References 4:

Grant Support:

Keywords: CIDP, Anti-MAG antibodies

Imlifidase In Patients With Severe Guillain-Barré Syndrome – A Phase II Safety, Tolerability And Efficacy Study

Poster No:
P 340

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Introduction:
Guillain Barré syndrome (GBS) is a life threatening and disabling disease despite current standard-of-care. Imlifidase is an immunoglobulin G (IgG)-degrading enzyme with strict specificity towards all four human subclasses of IgG. GBS patients may benefit from early treatment with imlifidase by depleting pathological IgG antibodies, and thereby disrupt disease progression resulting in quicker recovery and less severe disease as compared to standard-of-care. Objective: To investigate the efficacy, safety and PK/PD of imlifidase therapy in combination with IVIg in GBS patients.

Methods:
This is an open-label, single arm, multi-center, 1-year follow-up, phase II trial in approximately 30 adult GBS patients diagnosed according to NINDS criteria (ClinicalTrials.gov, NCT03943589). Onset of weakness should be within 10 days prior to screening and the patient should have a GBS disability score of $\geq$3. Imlifidase is administered as a single intravenous dose of 0.25 mg/kg over 30 min, given within 12 days of onset of weakness. IVIg, 0.4 mg/kg/day for 5 days, is started 48 hours later. Efficacy outcome measures include GBS Disability Score, R-ODS scale and MRC sum score, which are collected frequently throughout the study. PK/PD measurements are done for the first 16 patients included in the trial. The study will compare the efficacy of imlifidase to matched GBS patients from the International GBS Outcome Study (IGOS, ClinicalTrials.gov, NCT01582763).

Results:
The study is performed at 10 sites in France, the Netherlands and UK. To date (December 2022) 25 patients have been treated at 7 sites. Preliminary data on the first 16 patients enrolled show that imlifidase has been well tolerated without any infusion related reactions and that the PD profiles are similar to previous data in other patient populations.

Conclusions:
Study design, final PK/PD data and available safety data on all patients will be presented at the meeting. Final results are expected in 2024.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: Professors S. Attarian, P. van Doorn, B. Jacobs, D. Cornblath, H. Willison have consultancy agreements with Hansa Biopharma AB.

Keywords: imlifidase, Guillain Barré syndrome , clinical trial, IGOS, IgG antibodies

Rationale Behind Combining Imlifidase And IVIg Dosing Regimen In Patients With Severe Guillain-Barré Syndrome

Poster No:
P 341

Authors:
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Introduction:
This is an open-label, single arm, multi-center, international, 1-year phase II trial in 30 adult GBS patients with GBS-DS ≥3 (ClinicalTrials.gov, NCT03943589) combining for the first time imlifidase with standard IVIg treatment in GBS patients. The efficacy of imlifidase will be compared to matched GBS patients from the International GBS Outcome Study (IGOS, ClinicalTrials.gov, NCT01582763). We describe the rationale for the study design to overcome various challenges.

Methods:
Key challenges 1. IVIg is a substrate for imlifidase. Can imlifidase and IVIg be administered safely while ensuring the efficacy of both drugs? 2. Anti-imlifidase antibodies (ADA) are present in IVIg as most individuals will have been exposed to Streptococci. ADA may influence efficacy and safety.

Results:
Imlifidase is a novel treatment that rapidly cleaves immunoglobulin G. Within a few hours after dosing, the entire intra- and extravascular IgG pool is fully cleaved into F(ab')2 and Fc fragments. IVIg is started 48 hours after dosing imlifidase when circulating level of imlifidase is low. By delaying start of IVIg, the effect of imlifidase is maintained while the interaction between the two treatments is minimized. As IVIg is shown to be effective when started within 2 weeks of onset of disease, patients are dosed with imlifidase within 12 days of onset of weakness. Initially, the first IVIg infusion was given over >12 hours to minimize potential infusion related reactions. Since there were no observed adverse reactions in the first 16 treated patients, a standard IVIg infusion rate was used after amending the protocol. Initial results indicate that only the first IVIg dose is minimally cleaved by imlifidase.

Conclusions:
IVIg treatment can be initiated 48 hours after administration of imlifidase without concerns regarding efficacy or safety. IVIg remain as intact IgG with only a very small part of the first dose converted to single cleaved IgG.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: Professors S. Attarian, P. van Doorn, B. Jacobs, D. Cornblath, H. Willison have consultancy agreements with Hansa Biopharma AB.

Keywords: imlifidase, Guillain Barré syndrome , clinical trial, IGOS, IVIg

The Challenge Of Immunotherapy For Guillain-Barre Syndrome In Under-resourced Regions- Documented First Use Of Intravenous Immunoglobulin In Ghana.

Poster No:
P 342

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Introduction:
The clinical course of Guillain–Barré syndrome (GBS) in individual patients is highly variable. Early intravenous immunoglobulin (IVIG) accelerates recovery and diminishes the long-term neurologic disability. However, IVIg and its alternative plasma exchange, are costly and not easily available, even in the metropolis hospitals of Ghana.

Methods:
We present a case of severe GBS, whom we believe benefitted from timely IVIG treatment.

Results:
A 32-year-old male was admitted with a two-day history of paresthesia and weakness of both the upper and lower limbs. The symptoms progressed to include dysphagia and slurred speech; but bladder and bowel were not involved. Examination revealed flaccid dysarthria, impaired gag reflex, bilateral facial nerve palsy of lower motor neuron type, symmetric, areflexic flaccid quadriparesis (power of 2/5 in upper limbs and 1/5 in the lower limbs). Lumbar puncture revealed cytoalbuminologic dissociation. Nerve conduction study revealed a demyelinating neuropathy. Patient was bedridden and needed constant nursing care. He then developed respiratory failure requiring invasive ventilation. Patient could afford the USD $8,064 for a course of IVIG (0.4mg/kg daily for 5 days) which was started on day 4 of illness. He was also given anticoagulation prophylaxis and physiotherapy started. Patient had mild motor improvement and was out of respiratory failure after 2 weeks. At 3 months post discharge, patient was able to move without support with only mild symmetric distal extremity weakness.

Conclusions:
The patient had severe life threatening GBS. We believe IVIG shortened the course and severity of illness. This case again reiterates the need to make standard therapy for GBS, IVIG and plasma exchange, more accessible globally. In their absence in developing countries, we should seek evidence for the efficacy of alternative, less costly and more accessible treatments for example small volume plasma exchange.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Guillain-Barre Syndrome, Intravenous Immunoglobulin, Bilateral facial nerve palsy

Spinal schistosomiasis- A mimic of GBS in Africa

Poster No:
P 343

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Introduction:
In the developing world infectious disorders are important differential diagnoses of Guillain–Barré syndrome (GBS).

Methods:
Description of a 14-year-old Nyamwezit girl at Moshi, Tanzania, who presented with ascending flaccid lower limb weakness, numbness and incontinence over 5 days.

Results:
The patient's preceding febrile illness, diarrhoea and complete lack of pyramidal signs prompted consideration of GBS. As this was an under-resourced region, spinal MRI was not readily available to rule out the differential diagnosis of acute thoracic-conus medullaris myelopathy. Systemic evaluation revealed marked eospinophilia. (4.41 x10^ 9/L) Spinal tap showed raised protein (1135.10 mg/l) and reduced glucose (2.51 mmol/l) . The patient could not afford quantification of spinal fluid cells. A presumptive diagnosis of hydatid or acute schistosomiasis was made and patient was started on high doses of praziquantel, albendazole and corticosteroids. Intravenous immunoglobuins and plasma exchange, standard therapy for GBS elsewhere, are not available in Tanzania. MRI spine was eventually done on day 14 of illness. It showed hyperintense T2 signal from T1 downwards, suggestive of syringomyelia, and an enhancing mass. Biopsy of the mass was initially suspected to be astrocytoma WHO grade 1 but a review indicated schistosoma myelitis.

Conclusions:
Patient responded to further anti-helminthic therapy (albendazole, 5 days; Praziquantel,1 month) and corticosteroids (prednisolone 60mg a day, 3 weeks followed by dexamethsone 4mg twice a day, 1 week). The eosinophil count dropped to 0.6 x10^9 /l. She could only afford 2 months of physical therapy; after which her leg strength improved to MRC 2 to 3 and she was able to walk with assistance. Infectious diseases like Schistosomiasis as well as Diphtheria, Tetanus, Botulism and Paralytic Rabies are key mimics of GBS in the developing world.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: NIL

Keywords: GBS, Schistosomiasis, Inflammatory neuropathy

Olfactory Mucosa Mesenchymal Stem Cells secretome and Biomaterials Reveal New Paths to Peripheral Nerve Regeneration

Poster No:
P 344

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Introduction:
Despite recent advances in promoting peripheral nerve regeneration after injury, it has not yet been possible to establish an alternative treatment to supplant traditional surgical methods as gold-standard approaches [1]. Regenerative medicine, a therapeutic field alternative to conventional treatments, drew attention due to its versatility, multifactorial approach, and potential to revolutionize different medical fields, including Peripheral Nerve Injury (PNI). Among all options, the combination of cell-based therapies with biomaterials has been the most promising [2]. More recently Cell secretome has been explored as a cell-free technique with high scientific and medical interest for Regenerative Medicine [3].

Methods:
Previously our research group has extensively studied the functional characteristics of olfactory mucosa mesenchymal stem cells (OM-MSCs), a type of MSCs with a high therapeutic potential for the promotion of nerve regeneration after PNI [4]. In this work, the secretome produced and collected from Olfactory Mucosa Mesenchymal Stem Cells and Olfactory Ensheating Cells was therapeutically applied to promote peripheral nerve regeneration. Initially the conditioned medium (CM) was analyzed. Subsequently, CM was applied to sciatic nerves of rats after neurotmesis, using Reaxon® as tube-guides. The animals underwent periodic functional assessments and the sciatic nerves and cranial tibial muscles were evaluated stereologically and histomorphometrically, respectively.

Results:
The results obtained allowed to confirm the beneficial effects resulting from the application of this therapeutic combinations. The administration of conditioned medium from OM-MSCs led to the best results in motor performance, sensory recovery, and gait patterns. Stereological and histomorphometric evaluation also revealed the ability of this therapeutic combination to promote nervous and muscular histologic reorganization during the regenerative process.

Conclusions:
The therapeutic combination discussed in this work shows promising results and should be further explored to allow establishing the use of cell secretome as a new therapeutic application in the treatment of peripheral nerves after injury.

References:

Yes

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Grant Support: The author Rui D. Alvites acknowledges the Centro de Estudos de Ciência Animal (CECA), Instituto de Ciências, Tecnologias e Agroambiente (ICETA), Porto University (UP), and Fundação para a Ciência e Tecnologia (FCT) for the funding and availability of all

Keywords: Peripheral Nerve Injury, Mesenchymal Stem Cells , Biomaterials , Secretome , Animal Models

Guillain-Barre Syndrome as the first manifestation of systemic lupus erythematosus

Poster No:
P 345

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Introduction:
Guillain-Barre syndrome (GBS) is acute onset immune-mediated polyradiculoneuropathy. Systemic lupus erythematosus (SLE) is an autoimmune disease affecting multiple organs and systems including the central and peripheral nervous system. However, GBS as the first presentation of lupus is a rare condition. Herein, we report a case that manifested GBS as the primary presentation of SLE.

Methods:
A 70-year-old man came to our clinic complaining of a 3-weeks history of limb weakness. He had a medical history of hypertension, dyslipidemia, and diabetes mellitus. However, he had no antecedent infection. His symptoms began in the bilateral lower extremities 3 weeks ago and progressed to the bilateral upper extremities. Neurologic examination revealed weakness in the upper and lower extremities and normoactive deep tendon reflex. A Nerve conduction study showed acute inflammatory demyelinating polyneuropathy. A cerebrospinal fluid study revealed albunimocytologic dissociation. The anti-ganglioside antibody assay was all negative. Laboratory tests revealed hypo-osmolar hyponatremia and positive FANA (1:320), and low C3 and C4 level. Urine analysis revealed proteinuria (4+).

Results:
Intravenous immunoglobulin was administered at 0.4g/kg/day for 5 consecutive days. His symptoms were partially improved after treatment. However, his symptoms worsened 10 days after treatment. Limb weakness was aggravated and L-tube feeding was started due to dysphagia. In addition, he was transferred to the department of nephrology due to acute kidney injury. He was diagnosed with lupus nephritis and treated with steroid pulse therapy followed by oral steroids. After then, his weakness gradually improved and fully recovered 4 months later.

Conclusions:
In conclusion, GBS may occur in patients with SLE. Even it could be manifested as the first manifestation of SLE. Further investigation would be needed to identify the underlying etiology if patients with GBS had no antecedent infection or obvious triggers. Conventional GBS treatment may be insufficient to treat GBS with SLE and could need further immunosuppression treatment.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Guillain-Barre syndrome, systemic lupus erythematosus, lupus nephritis, intravenous immunoglobulin

CISP

Poster No:
P 346

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Introduction:
CISP(Chronic immune sensory polyradiculopathy) is an under recognized condition believed to lie within the spectrum of CIDP and similar to CIDP it responds to immunotherapy (eg- IVIG , prednisolone).

Methods:
Background- CIDP is a symmetrical proximal and distal weakness with sensory loss that progresses slowly or relapses over 8 weeks; motor>sensory involvement. Distinct features of CISP : Cutaneous sensory loss with sensory ataxia in the absence of motor involvement Isolated inflammatory Involvement of sensory roots proximal to Dorsal root ganglion hence normal Nerve conduction studies. Objective- To describe a case of CISP resulting in recurrent falls and highlight this uncommon, yet important and treatable cause of peripheral sensory ataxia with normal routine NCS. Our patient is a 80 year who was previously healthy. He has been suffering with 2 months history of sub-acute progressive numbness in hands and feet. Neurological examination- Positive findings-diffuse hyporeflexia in UL/LL, very mild proximal weakness in LL, bilateral severe proprioceptive loss and vibration loss in LL, severely ataxic gait; Negative findings-UL sensation normal, babinski sign absent, no bladder/bowel/Cranial nerve involvement or cerebellar signs, normal pupils. Clinical diagnosis=CIDP and differential diagnosis-sensory neuronopathy ; however NCS were normal suggesting a more proximal lesion.

Results:
The following Rx was instituted(duration over 2 months): IVMP, F.b IVIG 2g/kg over 5 days and PO Prednisolone 40mg OM, F.B 2 IVIG 2g/kg over 5 days, F.B PO Prednisolone 60mg X 4 weeks, F.B 3. IVIG 2g/kg over 5 days F.B PO Prednisolone 55mg x 4weeks +PO MMF 500mg BD. Gradual and slight improvement of symptoms was observed over 2 months of the above Rx regimen. Berg Balance Scale improved from 31/56 to 39/56.

Conclusions:
Conclusion: CISP is an uncommon, probably under-recognized and treatable cause of peripheral sensory ataxia. Having a high index of suspicion with early recognition and institution of appropriate immunotherapy possibly leads to better outcomes.

References:
Yes

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References 3:
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References 4:
Gosselin S, Kyle RA, Dyck PJ. Neuropathy associated with monoclonal gammopathies of undetermined significance. Ann Neurol 1991;30:54 – 61

Grant Support: Clinical Case

Keywords: A CASE OF PERIPHERAL SENSORY ATAXIA CAUSING RECURRENT FALLS"

Unique Commercially Available Multiparametric Anti-Ganglioside Antibodies ELISA Complying With New Regulatory IVDR Standards

Poster No:
P 347

Authors:
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Introduction:
In Vitro Diagnostic Device Regulation (IVDR) is the new harmonized EU regulatory framework to ensure safety and performance of in vitro diagnostics (IVD). Prominent IVDR aspects include scientific validity of the analyte and traceability. The anti-Ganglioside antibodies ELISA is the only commercially available multiparametric IVD-test to determine antibodies causing autoimmune-related neuropathies. It has been validated according to stringent IVDR-standards.

Methods:
The analytical performance was performed for IgG & IgM isotypes on the anti-Ganglioside antibodies ELISA. Within-laboratory precision and within-run repeatability were assessed with 20days*2runs*2replicates (n total=80wells), reproducibility with 3instruments/lots/operators*5days*1run*5replicates (n total=75wells). The analytical sensitivity (LoB & LoD) was investigated using four serum samples. Clinical sensitivity and specificity was derived from six published studies, based on the current IVD. The method comparison between IVDR & current IVD with 56 serum included Passing-Bablok and Bland-Altman analysis.

Results:
Within-laboratory precision (total) %CV was ≤36.5% (range 5.7–36.5%). Repeatability (within-run) %CV was ≤19.2% (range 2.0–19.2%). Reproducibility (total) %CV was ≤33.2% (range 7.7–33.2%). Analytical sensitivity: LoB: <14.2 %Ratio; LoD: <27.1 %Ratio. Cut-off: ≤50 %Ratio. The mean clinical sensitivity was 63% (95%CI: 44–82%), the mean clinical specificity was 82% (95%CI: 70–94%). The mean bias (Bland-Altman) between the current and IVDR version, is 0.6-15.7%(IgG) and 5.7-21.6%(IgM) for the common five neural antigens. The slope calculated by Passing-Bablok ranged from 1.03-1.08(IgG) and 0.77-1.15(IgM) with an intercept from 0.13-0.51(IgG) and 0.04-0.85(IgM).

Conclusions:
The anti-Ganglioside antibodies ELISA meets IVDR standards, is comparable to the current version and is thus a true alternative for in-house tests.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: in vitro diagnostic autoimmune assay, anti-ganglioside antibodies, Regulatory IVDR Standards, immune-mediated neuropathies, rare autoimmune-disease

Measuring A Case Series With A Unique Commercially Available Anti-Ganglioside Antibodies ELISA

Poster No:
P 348

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Introduction:
There are >500 causes for a peripheral neuropathy and >200 mimicking disorders e.g. other neurological or autoimmune diseases. ELISA is frequently used as a reliable and sensitive method to determine anti-neural antibodies confirming an autoimmune etiology, justifying appropriate treatment. The only commercial multiparametric anti-Ganglioside antibodies ELISA that meets In Vitro Diagnostic Device Regulation (IVDR) standards allows for specific detection of neural antibodies.

Methods:
Current and IVDR-version, six different neural antigens each, were compared measuring a case series of 56 serum samples. The overall-agreement between the IVD-test-versions was calculated in addition to the assignment of the results to one of three categories (negative, grey zone, positive) for IgG and IgM isotypes.

Results:
The overall-agreement between the IVD-test-versions was 95-100% (IgG & IgM). The case series resulted in 6x56=336 data-points. Case series: apparently healthy blood donors (n=16) and incubation buffer (n=3) as negative controls, control group (n=16) with other neurological or autoimmune diseases and anti-neural antibody positive (≥1anti-neural antibody) serum samples (n=21). ≥96% of apparently healthy controls and 92% of the control group were negative (<30 %Ratio) for IgG&IgM. Expectedly ≤5% of all samples fall in the grey-zone (30-50 %Ratio). ≤7% of the control group and ≤13% of anti-neural antibody positive samples were positive (>50 %Ratio). Many positive samples display distinct binding and are negative (<30 %Ratio) for some of the six structurally different antigens.

Conclusions:
The investigated commercial multiparametric anti-Ganglioside antibodies ELISA justifies a distinct grey-zone in addition to seronegative and -positive samples. The two compared regulatory versions are in perfect agreement. The IVDR version is a suitable tool for laboratories that need to comply with new and more stringent regulatory standards.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: in vitro diagnostic autoimmune assay, anti-ganglioside antibodies, Regulatory IVDR Standards, immune-mediated neuropathies, rare autoimmune-disease

Outcome Measures for Patients with Chronic Inflammatory Neuropathy: Lessons from Patient Focus Groups

Poster No:
P 349

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Introduction:
Chronic Inflammatory Neuropathies are a group of disabling autoimmune neuromuscular disorders that can result in reduced quality of life and impairment in daily activities. Outcome measures are important for tracking progression and response to treatment. Value Based Health Care frameworks emphasize the importance of delivering care that improves health outcomes that matter to patients, the experience of receiving care, and the effectiveness and efficiency of care. Teisberg et al. propose focusing on measures that evaluate patient priorities: 'Capability, Comfort, and Calm'. The purpose of this study was to broadly understand patients' lived experiences and the outcome measures that are most meaningful to them.

Methods:
Nine participants with a diagnosis of chronic inflammatory demyelinating polyneuropathy or multifocal motor neuropathy took part in focus groups. The focus groups were conducted virtually using a semi-structured guide and assessed participants' experiences with the disease and outcomes that are most meaningful to them. Themes were freely explored as they emerged. Thematic analysis using an inductive coding approach identified themes mapped to 'Capability, Comfort, and Calm'.

Results:
Participants focused on five primary themes: (1) fear and uncertainty (Calm, Comfort), (2) physical and psychological challenges (Comfort, Capability) (3), illness variability (Comfort, Capability), (4) interaction with the healthcare system (Calm), and (5) resilience (Calm, Capability). The themes illustrated the challenges participants' face due to the disease, and highlighted possible areas of improvement in the patient journey. Participants identified measures of psychosocial health, balance, gait, and daily activities as important.

Conclusions:
Listening to the patient perspective during the development and implementation of an outcome panel provides insights into which outcomes matter most to patients and informs shared decision-making. The mapping of themes onto Capability, Comfort, and Calm categories helped refine recommendations for implementing meaningful outcome measures in clinical practice. Implementing recommendations may improve the ability to provide high-value and patient-centred care.

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Yes

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References 2:

References 3:

References 4:

Grant Support: Supported by the Mahon Family Foundation.

Keywords: outcome measures, chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy, value-based healthcare, qualitative study

Does the serum and CSF cytokine dosage differ between post-infectious and para-infectious SARS-CoV-2-related Guillain-Barré Syndrome?

Poster No:
P 350

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Introduction:
Guillain–Barré syndrome (GBS) is an acute postinfectious immune-mediated polyneuropathy. The pathogenic hypothesis comprises virus-related neuropathogenic mechanisms and hyperacute immune response. We explored the hypothesis of a hyperacute immune response by dosing cytokines on CSF and serum of patients with SARS-CoV-2-related GBS.

Methods:
Twentysix patients with SARS-CoV-2-related GBS were divided in two groups: 1) 'classic onset', if they developed GBS 7 days after the onset of the infection, 2) 'parainfectious onset', if they developed GBS before 7 days from the onset of the infection. We dosed cytokines (IL-1b, IL-6, IL-8, TNF-alpha) on CSF and serum and compared the dosages in both groups, also correlating the dosage of each cytokine with the severity of both infection and GBS, both at onset and at last follow-up.

Results:
Fifteen patients were listed in the 'classic onset' group (F = 6, mean age 62) and 11 in the 'parainfectious onset' group (F = 4, mean age 62). Sixteen patients developed COVID-19 pneumonia, 9 developed upper respiratory tract infection and 1 developed gastrointestinal symptoms; 7 were admitted in ICU, 8 were not hospitalized. The mean GBS disability scale (GBS-DS) was 4 at onset and 2 at follow-up. We found no difference in the total amount of cytokines in serum and CSF between the two groups. Furthermore, no correlation was found between the dosage of each individual cytokine and severity of SARS-CoV-2 infection, the GBS-DS at onset and the GBS-DS at follow-up.

Conclusions:
The presence of a hyperacute immune response is one of the hypotheses underlying the genesis of parainfectious GBS. Our observations showed that there are no significant differences in the amount of cytokines in patients with 'parainfectious onset' of GBS when compared with 'classic onset'. It can be concluded that the cause of the parainfectious onset must be another, and further studies are needed to evaluate other hypotheses.

References:

No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: cytokine, Guillain-Barré Syndrome, Hyperacute immune response

In vitro generation of disease-associated autoantibodies from patients with an aggressive, highly lethal atypical inflammatory neuropathy

Poster No:
P 351

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Introduction:
Autoantibodies targeting both nodal/axonal neurofascin-186 (NF186) and paranodal/glial neurofascin-155 (NF155) are associated with a clinically distinct, severe, and rapidly progressive inflammatory 'pan-neurofascin' (panNF) neuropathy. Although B-cell depletion improves some patients' symptoms, revealing a central role for B cells in disease pathogenesis, others do not improve or subsequently relapse. Before the B-cell population(s) responsible for autoantibody production can be determined, a protocol is required to reliably generate autoantibodies from peripheral blood mononuclear cells (PBMCs) in culture.

Methods:
Culture conditions were tested using healthy control (HC) PBMCs to maximise total IgG production as measured by ELISA. $CD27^+CD38^+$ plasma cell generation was assessed using flow cytometry. ELISA, along with a transiently-transfected, cell-based assay, were used to evaluate total, NF155, and NF186 IgG production from bulk unsorted and sorted $NF155^+$ and $panNF^+$ patient cell cultures. B cells were sorted into new emigrant, mature naïve, and unswitched and switched memory subpopulations using FACS.

Results:
$2x10^5$ PBMCs/well bulk cultured for 14 days with Resiquimod (R848), interleukin-2 (IL-2), and soluble CD40 ligand (sCD40L) in a supplemented B-cell media consistently produced total IgG concentrations ranging from 2-25 μg/mL. This was supported by expansion of $CD27^+CD38^+$ plasma cells after six days. These conditions did not elicit antigen-specific IgG production from sorted or unsorted $NF155^+$ or $panNF^+$ patient PBMCs, nor total IgG production in new emigrant or mature naïve subpopulations. However, the addition of IL-1β, IL-21, and TNFα stimulated total IgG production in all subpopulations from HCs.

Conclusions:
Our data demonstrate that IL-1β, IL-21, and TNFα are necessary in addition to R848, IL-2, and sCD40L to stimulate total IgG production in four major HC B-cell subpopulations. Ongoing work will investigate the effect of these additional cytokines on NF155 and NF186 IgG production in fractionated $panNF^+$ patient cultures, whose resulting autoantibodies can be further investigated to clarify the underlying disease immunopathology.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: B cell, inflammation, neurofascin, neuropathy, autoantibodies

Chronic inflammatory demyelinating polyneuropathy with phrenic nerve involvement leading to respiratory failure

Poster No:
P 352

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Introduction:
Chronic inflammatory demyelinating polyneuropathy (CIDP) is an acquired inflammatory neuropathy, potentially treatable. Various subgroups of CIDP have been identified including the pure motor variant. Phrenic nerve palsy has rarely been reported in association with CIDP. Nevertheless, its clinical awareness and timely diagnosis are paramount to facilitate appropriate management with ventilatory assistance.

Methods:
Four patients with overt CIDP and phrenic nerve involvement were identified in our department of clinical neurophysiology. Three of them experienced respiratory failure requiring ventilatory assistance

Results:
Here we report 4 patients, 2 mans and 2 females, aged between 25 and 69 years who presented with weakness of the four limbs consistent with pure motor CIDP in 3 cases and typical CIDP in one. The clinical course was progressive in two patients of acute GBS-like onset and relapsing in one each. In addition to the electrophysiological criteria of demyelinating polyneuropathy, the phrenic nerve involvement was documented in the four cases. However, three patients were symptomatic with respiratory failure. The latter have motor variant of CIDP with a poor outcome despite a period of significant improvement following appropriate treatment.

Conclusions:
Clinical ventilatory dysfunction in CIDP is unusual finding. It may be an indicator of poor prognosis and the phrenic nerve involvement is frequent but underdiagnosis. Phrenic nerve conduction studies should be more routinely done to timely look for and manage respiratory impairment.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: CIDP, Phrenic nerve, Respiratory failure, ENMG

A case of chronic inflammatory demyelinating polyneuropathy misdiagnosed as entrapment syndromes

Poster No:
P 353

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Introduction:
Chronic inflammatory demyelinating polyneuropathy (CIDP) is an immune-mediated peripheral nerve disorder and treatable. CIDP is not associated with increased frequency of demyelination at entrapment sites. We report a case of CIDP misdiagnosed as entrapment syndromes in which neurological symptoms were completely recovered by steroid treatment.

Methods:
We retrospectively reviewed medical record of the patient.

Results:
A 27-year-old woman presented with bilateral arm weakness for two months. Five years ago, the left wrist drop occurred and four months ago, after wearing a baby carrier, right arm weakness occurred. And the symptoms improved without treatment. Two months ago, numbness and weakness in left hand occurred, and similar symptoms occurred in right hand. And three days ago, after her baby slept on her right arm, she developed right wrist drop. Neurological examination revealed distal dominant asymmetrical arm motor weakness with hyporeflexia. Significant hypo-esthesia was observed in her fingers and palm. In motor nerve conduction study (NCS), conduction blocks were observed. Sensory NCS was abnormal on bilateral median nerves. Considering the possibility of hereditary neuropathy with liability to pressure palsies (HNPP), we checked PMP 22 gene study and it was normal. After one month, tongue deviation to left occurred. Follow-up NCS revealed demyelinating features at all motor nerves and met the 2010 EFNS/PNS criteria of CIDP. She was treated with methylprednisolone (500mg/day) for three days, and her symptoms were significantly improved. She is under close observation at outpatient department while taking oral steroid and azathioprine. In the follow-up NCS performed three months later, the conduction block was improved.

Conclusions:
Even if there is recurrent history of compressive neuropathy, a diagnosis other than HNPP should be fully considered for prompt treatment.

References:
Yes

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Rajabally, Yusuf A., and Manisha Narasimhan. 'Electrophysiological entrapment syndromes in chronic inflammatory demyelinating polyneuropathy.' Muscle & nerve 44.3 (2011): 444-447.

References 2:

Joint Task Force of the EFNS and The PNS. 'European Federation of Neurological Societies/Peripheral Nerve Society guideline on management of chronic inflammatory demyelinating polyradiculoneuropathy: report of a joint task force of the European Federation

References 3:

References 4:

Grant Support:

Keywords: CIDP, HNPP, PMP22 gene, entrapment syndrome, nerve conduction study

Clinical relevance of distinguishing autoimmune nodopathies from CIDP: longitudinal assessment in a large cohort

Poster No:
P 354

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Introduction:
Objective: To determine treatment response and whether treatment response is associated with antibody titer change, in autoimmune nodopathy (AN) patients that were initially diagnosed as chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), and to compare clinical features and treatment response between both groups.

Methods:
Serum IgG antibodies to neurofascin-155 (NF155), contactin-1 (CNTN1), and contactin-associated protein 1 (CASPR1) were detected with cell-based assays in patients diagnosed with CIDP. Clinical improvement was determined using the modified Rankin scale (mRS), need for alternative and/or additional treatments, and assessment of the treating neurologist.

Results:
We studied 401 patients diagnosed with CIDP and identified 21 patients with autoimmune nodopathy (10 anti-NF155, 6 anti-CNTN1, 4 anti-CASPR1, and 1 anti-NF155/anti-CASPR1 double positive). In patients with paranodal antibodies ataxia (68% vs. 28%, p=0.001), cranial nerve involvement (34% vs. 11%, p=0.012), and autonomic symptoms (47% vs 22%, p=0.025) were more frequently reported; AN patients improved less often after IVIg treatment (39% vs 80%, p=0.002) and required additional/alternative treatments more frequently (84% vs 34%, p<0.001), compared to CIDP patients. Antibody titers decreased or became negative in patients improving on treatment. Treatment withdrawal was associated with a titer increase and clinical deterioration in four patients.

Conclusions:
Distinguishing CIDP from autoimmune nodopathy is important, as patients with autoimmune nodopathy seem to need a different treatment approach. Improvement and relapses were associated with changes in antibody titers, underlining the pathogenicity of these antibodies.

References:

No

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References 4:

Grant Support: This study was funded by the Dutch Prinses Beatrix Spierfonds (grant number: W.OR16-18)

Keywords: autoimmune nodopathies, CIDP, paranodal antibodies

IgM Anti-GM1 Antibodies and Complement Activation in an iPSC-derived Disease Model for Multifocal Motor Neuropathy

Poster No:
P 355

Authors:
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Introduction:
Multifocal motor neuropathy (MMN) is a rare, chronic immune-mediated neuropathy characterized by progressive asymmetric weakness mainly affecting hands and forearms and lower legs. MMN is associated with increased titers of IgM antibodies against the ganglioside GM1, which are found in serum from 50-75% of MMN patients. One pathogenetic hypothesis is that these antibodies bind to the axolemma at nodes of Ranvier, interfere with axon-Schwann cell (SC) interactions, and cause disruption of ion channels at the (peri) node and ultimately axonal damage. Complement activating properties of anti-GM1 IgM antibodies correlate with clinical features, including weakness and axonal damage.

Methods:
We investigated IgM anti-GM1 binding and complement activation in a pluripotent stem cell-derived motor neuron (MN) and SC-line disease model for MMN using serum samples from a large cohort of patients. We characterized these cells for the expression of complement receptors and membrane-bound regulators.

Results:
MNs express CD46, CD55, and CD59, which intrinsically protected these cells against anti-GM1 IgM-induced complement-mediated lysis. MNs also express C3aR, C5aR, and CR1. Sera from 50 out of 102 (49%) MMN patients showed increased anti-GM1 IgM titers as determined by standardized ELISA. We observed a strong association between anti-GM1 antibody titers and IgM binding to MNs. Importantly, we observed significant higher IgM binding in patients without detectable anti-GM1 antibodies with ELISA, compared to healthy controls. Addition of fresh human serum to opsonized MNs resulted in increased C3 fixation in both seronegative and seropositive patients, which correlated to anti-GM1 IgM antibody binding. Also, C5a formation was detected.

Conclusions:
Our results emphasize the role of IgM anti-GM1 and complement in the pathogenesis of MMN in a larger percentage of patients than expected. By expressing CD59, MNs are protected against complement-mediated lysis. Since MNs express C3aR, their function and integrity may also be affected by complement components upstream of membrane attack complex formation.

References:
No

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References 4:

Grant Support:

Keywords: Multifocal Motor Neuropathy, Complement, IgM anti-GM1, anti-ganglioside antibodies, iPSC-derived motor neurons

Anti-HEV Antibody Status In Patients Affected By Chronic Inflammatory Demyelinating Polyneuropathy: A Prevalence Study

Poster No:
P 356

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Introduction:
Hepatitis E virus (HEV), a RNA virus with oro-faecal route of transmission, is known as a possible risk factor in Guillain-Barrè syndrome (1). Recent studies have evidenced that respiratory and gastrointestinal infections can be a trigger factor in Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) (2). The aim of this study is to assess the prevalence of recent or history of HEV infection in CIDP patients, performing a correlation study between CIDP and exposure to risk factors for HEV infection and considering the possible influence of administered therapies on the prevalence data.

Methods:
45 patients CIDP subjects were recruited from three Neuromuscular Centers. Patients filled a questionnaire about demographic and anamnestic variables, lifestyle and food habits, previous trips and blood products therapy. Patients were subjected to blood tests to anti-HEV IgG detection and, if positive, to anti-HEV IgM and RT-PCR for searching HEV-RNA. 301 blood donors were analyzed as control subjects.

Results:
The prevalence of anti-HEV IgG in CIDP patients, matched for sex and age with control sample, was 33.33%, with OR 4.34 (p=0.00003). Previous blood transfusions (p=0.08), working closely with animals (p=0.06) and eating liver sausage (p=0.06) approached to statistical significance with IgG seropositivity. Steroids and/or azathioprine therapies didn't correlate with anti-HEV IgG positivity, representing an independent factor.

Conclusions:
This study showed a greater IgG-HEV prevalence in CIDP patients compared to general population, although is not able to demonstrate HEV causal effect in this pathology. By searching in protein and nucleic acid databases, we also found significant antigenic homologies between HEV and some myelin proteins (3), possibly due to molecular mimicry mechanism between viral capsid protein/RNA polymerase and myelin/nodal-paranodal protein aminoacid sequences, similarly to another study that showed common aminoacid sequences between Zika Virus and some proteins implicated in demyelinating and axonal neuropathies (4).

References:
Yes

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Grant Support:

Keywords: HEV, CIDP, PREVALENCE, ANTIBODIES, MOLECULAR MIMICRY

Testing Specificity And Sensitivity Of Different Existing Fluid Biomarkers In Polyneuropathies: Clinical Relevance And Limitation

Poster No:
P 357

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Introduction:
The term biomarker refers to 'a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention'. To this end, body fluid biomarkers display fundamental makings into the clinical practice, improving and accelerating diagnosis, monitoring disease activity and progression and evaluating therapeutic interventions. CIDP and GBS are among the neurological disorders in which, besides clinical and neurophysiological criteria, there are no effective, reliable and clinically acceptable biological markers. For neurological disorders cerebrospinal fluid (CSF) is a primary matrix for biomarker discovery, due to its direct contact with nervous system compartment.

Methods:
In this study, we have tested and compared some candidate available biomarkers described in literature that reflect different nerve component damages or pathological processes associated with polyneuropathy (demyelination, inflammation, axonal loss) to assess their potential application in the management of these diseases. We evaluated the levels of sphingomyelin (SM), interleukin-8 (IL-8), neurofilament light chain (NfL) in the CSF of at least 115 patients including stable and active CIDP, AIDP, axonal GBS, non-inflammatory axonal neuropathies and other neurological diseases used as controls.

Results:
CSF SM was higher in AIDP and CIDP in active stage compared with CTRL, axonal form of GBS (AMAN, AMSAN), non-autoimmune axonal neuropathies and CIDP in stable stage. CSF IL-8 differentiated GBS from CIDP, regardless of different form and stage of the diseases. CSF NfL were extremely variable in the same group of patients and, as supported by literature, proved to be a poor diagnostic and disease activity biomarker for GBS and CIDP.

Conclusions:
Both SM assay and IL-8 dosage, due to the typical simplicity and practicality, may apply for a routine use in the clinical practice. Utilizing these two biomarkers would greatly improve the management of these patients, especially avoiding misdiagnosis and costly and lifelong unnecessary treatments.

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Yes

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Grant Support:

Keywords: BODY FLUID BIOMARKERS, CSF, CIDP, GBS, CLINICAL PRACTICE

Peripheral Nerve Development And Neuromuscular Junction Maturation Are Altered By Gut Microbiota Depletion

Poster No:
P 358

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Introduction:
In the last decades, a growing interest in the study of the cross-talk between gut microbiota (GM) and its human host has been developed. The GM consists of a variety of symbiotic microorganisms (e.g., bacteria, fungi and others) and its composition, dependent on nutritional factors, has proven effects on healthy or pathological conditions in mammalian organisms. While the interaction between GM and organs such as gut, brain, liver and heart has been widely explored, its impact on the development of the peripheral nervous system and its functional connection to skeletal muscles, has up to now not been deeply investigated.

Methods:
Towards this aim, we analyzed dorsal root ganglia (DRG) and peripheral nerves, together with skeletal muscles, collected from newborn and adult mice with a complex gut microbiota (CGM), germ free (GF), and gnotobiotic mice (selectively colonized with 12 known gut microbe strains, OMM12).

Results:
Stereological and morphometrical analysis, demonstrated that the absence of gut microbiota affects the development of median nerves, resulting in smaller diameter and hypermyelinated axons in adult GF and OMM12 mice. In accordance, transcriptomic analysis of DRG and sciatic nerve samples revealed differentially expressed genes, pointing to an impaired development of peripheral nerves in GF compared to CGM mice. Moreover, myofiber size reduction was pronounced in newborn and adult GF muscles, when compared to CGM ones, while OMM12 appeared more similar to GF in newborn samples, and to CGM in adult ones. GM strongly impacts also on neuromuscular junctions (NMJs): newborn GF and OMM12 muscles displayed smaller NMJs compared to CGM, while adult GF NMJs did not show morphometric differences, but appeared more fragmented than CGM ones, pointing to altered denervation/re-innervation processes, as witnessed by the upregulated expression of denervation and regeneration markers.

Conclusions:
These data support the existence of a novel axis, mediating GM impact on the neuromuscular system.

References:
No

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References 3:

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Grant Support:

Keywords: Germ-free mice, Gnotobiotic mice, Nerve development, Myelin, Skeletal muscles

A single-center, retrospective study of ATTR-PN (transthyretin amyloidosis with polyneuropathy) clinical features in South Korea; Descriptive analysis

Poster No:
P 359

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Introduction:
ATTR-PN (transthyretin amyloidosis with polyneuropathy) is a progressive sensorimotor and autonomic neuropathy caused by amyloid deposition in the endoneurium due to misfolding of the transthyretin protein. Early diagnosis is challenging, so a timely diagnostic test is critical by discriminating red flag signs through detailed history taking and physical examination. Due to the lack of epidemiologic studies in South Korea due to its rarity and various features, we presented a single-center experience and compared it with prior studies.

Methods:
A retrospective cross-sectional study of all patients diagnosed with ATTR-PN was performed at single tertiary medical centers in Seoul, Korea. From January 2000 to February 2021, we analyzed the clinical characteristics and nerve conduction study of patients diagnosed with ATTR-PN, confirming the TTR gene mutation after exhibiting symptoms of neuropathy and cardiomyopathy.

Results:
A total of five patients (60% male) were collected. The onset age was 56.2±11.3 years, duration of the disease was 25.75±27.71 months. At ATTR-PN diagnosis, limb paresthesia was the most frequent symptoms in 3 patients (60%). The phenotype of all patients was a mixed type. As for the mutation type, Asp58Ala was the most common (40%). Sensory manifestation was the most common (100%), and pain, weakness (60%), genitourinary, and cardiovascular autonomic symptoms were observed (80%). The abnormal NCS findings were relatively high in DML, MCV in the median nerve, and FWL in the peroneal nerve. The average with abnormal values were 5.01±1.01ms, 41.77±8.10m/s, and 57.14±4.07ms. In sensory NCS, abnormal SCV values were slightly higher in median nerve.

Conclusions:
In our study, TTR mutation type and clinical characteristics were various in patients in South Korea. Asp38Val, known to be common to date, was not seen. However, the Asp58Ala was the most common, and Lys55Asn mutation was newly reported. The NCS finding is also highly heterogeneous, and a more extensive study will be needed.

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Yes

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Grant Support:

Keywords: ATTR-PN, transthyretin amyloidosis with polyneuropathy

TS-HDS Autoantibody: Clinical Characterization and Assessment of Clinical Utility

Poster No:
P 360

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Introduction:
We aim to establish clinical utility of trisulfated-heparin disaccharide (TS-HDS) IgM testing.

Methods:
Medical records of patients with positive TS-HDS antibodies who were evaluated at Mayo Clinic from 2009 to 2022 were reviewed. Immunotherapy responsiveness was evaluated based on improvement in inflammatory neuropathy cause and treatment (INCAT) disability score, modified Rankin Scale (mRS) or neuropathic pain.

Results:
Seventy-seven patients (50 females) had positive TS-HDS antibody. Median age at symptom onset was 48 (9-77) years. Median titer was 25,000 (range 11,000-350,000). Twenty-six patients (34%) did not have objective evidence of peripheral neuropathy. Nine patients (12%) had other known causes of neuropathy. Among the remaining 42 patients, half presented with subacute progressive course; the other half had chronic indolent course. Most common phenotypes were length-dependent peripheral neuropathy (n=20,48%), length-dependent small-fiber neuropathy (n=11,26%), and non-length-dependent small-fiber neuropathy (n=7,17%). Nerve biopsies showed epineurial inflammatory cell collections in 2 but no interstitial abnormalities in the remaining 7. The majority of intraepidermal nerve fiber densities (7/10), thermoregulatory sweat tests (12/21) and autonomic reflex screens (27/49) were normal. Post-immunotherapy improvement in mRS/INCAT disability score/pain was seen in 13/42 patients. Sensory ganglionopathy was associated with post-immunotherapy improvement (p=0.03) while length-dependent peripheral neuropathy pattern was associated with lack of immunotherapy response (p=0.03). TS-HDS IgM titers had low discriminative ability to identify immunotherapy response with an area under the curve (AUC) of 0.57.

Conclusions:
The diagnostic value of TS-HDS IgM as a biomarker in identifying and managing immune-mediated neuropathies is not substantiated. Decision on initiating immunotherapy should be based on highly suspicious clinical phenotype i.e., sensory ganglionopathy, rather than TS-HDS antibody positivity or titer.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: TS-HDS, autoimmune neuropathy, small fiber neuropathy, sensory ganglionopathy

Primary and Secondary Perineuritis: Case Report and Systematic Review of the Literature

Poster No:
P 361

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Introduction:
The perineurium surrounds each fascicle and forms part of the blood-nerve barrier. 'Perineuritis' refers to both a histopathological finding and specific clinicopathological entity, primary nonsystemic, nonvasculitic perineuritis (PNNP). We report a case of PNNP and review the literature.

Methods:
We searched PubMed, Embase, Scopus, and Web of Science for 'perineuritis.' These searches yielded 380 unique references. We selected 43 full-text English-language and 4 Japanese-language articles. Hand search yielded 167 additional full-text articles/chapters relevant to perineuritis.

Results:
Case: 63-year-old woman developed an acutely progressive, exquisitely painful, axonal, sensory-motor, overlapping multifocal neuropathy 2.5 years after breast cancer. Nerve biopsy revealed non-granulomatous, non-vasculitic perineuritis/endoneuritis. Muscle biopsy showed chronic endomysial/perimysial perivascular inflammation. MRI revealed enhancing obturator/femoral nerves. IVIg produced no immediate benefit, but she responded to corticosteroids/plasma exchanges. After 20 months, she had residual foot drop and numbness of torso/feet but no pain. Literature review: Searches yielded 20 cases (11M/9F) of PNNP: progressive, unexplained, nonsystemic neuropathy with biopsy showing non-vasculitic perineuritis. Patients ranged in age from 18-75 (mean 53.7) years and had symptoms 2-24 months before diagnosis. Neuropathy was usually sensory-motor (15/20), painful (18/19), multifocal (16/20), and distal-predominant (16/17) with legs affected more than arms. Truncal numbness occurred in 6/17. 55% had elevated CSF protein. EMG/NCS demonstrated primarily axonal changes. Nerve biopsies showed T-cell-predominant inflammation, widening, and fibrosis of perineurium; infiltrates in epineurium in 50% and endoneurium in 35%; and non-uniform axonal degeneration. Five had epithelioid cells. 19/20 received corticosteroids, 8 with additional immunomodulators; 18/19 improved. Two patients did not respond to IVIg. Outcome: 13/16 mild and 2/16 moderate disability; 1/16 died. Secondary causes of perineuritis include leprosy, vasculitis, neurosarcoidosis, neuroborreliosis, neurolymphomatosis, toxic oil syndrome, eosinophilia-myalgia syndrome, and rarer conditions.

Conclusions:
PNNP appears to be an immune-mediated, corticosteroid-responsive disorder. It mimics nonsystemic vasculitic neuropathy but is less well studied. Cases with epithelioid cells might represent PNS-restricted forms of sarcoidosis.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: perineuritis, multifocal neuropathy, inflammatory neuropathy, systematic literature review, peripheral nerve pathology

Rituximab Therapy in the treatment of Non-systemic Vasculitic Neuropathy: A Sri Lankan Experience

Poster No:
P 362

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Introduction:
Non-systemic vasculitic neuropathy (NSVN) is a peripheral neuropathy occurring in isolation without other organ involvement. Patients typically present with a progressive, painful, asymmetric, multifocal, distal predominant neuropathy. Electrodiagnostics reveal an axonal asymmetric polyneuropathy. High dose glucocorticoids are used in the initial management. Moderate to severe disease may require cyclophosphamide treatment. Rituximab appears to be a less toxic alternative in such instances.

Methods:
The purpose of this study is to highlight Rituximab as a therapeutic option for NSVN due to its efficacy, wide availability and relative low cost. A 46-year-old female patient presented with pain & numbness in her feet along with tingling sensation in her left hand. This progressed to weakness of the left hand. Electrodiagnostics revealed a mild left sided ulnar and median nerve palsy. A tentative diagnosis of mononeuritis multiplex was made and the work up for an underlying cause commenced. She responded well to oral corticosteroids. 3 months later, she re-presented with progressive worsening of the left upper limb weakness. Additionally, she now showed weakness of the right upper limb and both lower limbs. Repeat electrodiagnostics revealed new axonal type involvement of right sural, bilateral peroneal and the right median nerves. All investigations including a superficial radial nerve biopsy & vasculitic screening were unremarkable. Therefore, a clinical diagnosis of NSVN was made and she was treated with high dose corticosteroids.

Results:
The response to treatment was poor and significant worsening of symptoms occurred when oral prednisolone was tapered below 30mg daily. IV Rituximab was added at a dose of 500mg per dose, with 2-doses given 2-weeks apart. She responded well clinically and the dose of prednisolone was successfully reduced to 10mg daily.

Conclusions:
Rituximab appears effective and safe in the treatment of NSVN in developing countries like Sri Lanka where affordability plays a crucial role in the choice of immunomodulatory drug

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Rituximab, Vasculitic Neuropathy

Correlations of high-resolution ultrasonography and nerve conduction studies in demyelinating immune-mediated neuropathies

Poster No:
P 363

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Introduction:
Immune-mediated neuropathies are a complex a group of diseases. Treatment in the early stages is crucial to avoid sequelae but diagnosis can be challenging. High-resolution ultrasonography (HRUS) has been increasingly proven to be an interesting method for diagnosing. Here we present correlations between neuroconduction studies (NCS) and HURS in patients with demyelinating immune-mediated neuropathies.

Methods:
From july 2021 to july 2022, we selected patients with inflammatory demyelinating polyneuropathy. The diagnosis was established by clinical examination, neurophysiological patterns on previous exams, response to treatment and disease progression. The patients were submitted to NCS and HRUS. Motor NCS was performed on the median (wrist, antecubital fossa, axilla and Erb's point) and ulnar nerve (wrist, below and above elbow,axilla and Erb's point). CSA values were correlated with demyelination parameters from NCS.

Results:
Thirteen patients: 8 CIDP, 1 HIV-associated vasculitic neuropathy,1 anti-MAG neuropathy and 3 other demyelinating neuropathy were selected. The age range from 18 to 70 yo. Disease duration: from 6 months to 28 years. Twenty median and 24 ulnar nerves were assessed. All median (100%) and 23 ulnar nerves (95,8%) showed CSA increase some segment with 14 (70%) and 10 (41%) all segments were thickened respectively. Proximal segments and longer disease duration correlated to highest CSA values. Conduction block (CB) was observed in 9 median and 15 ulnar nerve with 6 median and 5 ulnar nerve the highest CSA value correspond to CB segment. CIDP showed the greatest thickening, particularly in the classic form, with sonographic appearance similar to anti-MAG neuropathy. One patient with the Lewis Sumner form had thickening only at the CB site. In HIV-related vasculitis neuropathy, CSA increase but it was lower than in CIDP.

Conclusions:
HRUS provides reliable information and seems to be complementary to NCS in demyelinating immune-mediated neuropathies. New parameters like nerve variability and fascicular analysis can improve this method.

References:
Yes

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Grant Support:

Keywords: High Resolution ultrasound, Inflamatory neuropathy, Neuroconduction Studies, CIDP

Update On The International Guillain-Barré Syndrome Outcome Study (IGOS)

Poster No:
P 364

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Introduction:
Guillain-Barré syndrome (GBS) is an acute immune-mediated polyradiculoneuropathy with a highly variable clinical course and outcome requiring better treatments. The International GBS Outcome Study (IGOS) is a prospective observational multicenter cohort study that aims to identify clinical and biological predictors of disease course and to provide a platform for comparative treatment studies.

Methods:
The IGOS Consortium consists of researchers and clinicians from 21 countries across 5 continents. All patients within the diagnostic spectrum of GBS are included irrespective of age, disease severity and treatment, within two weeks from the onset of weakness. Data are collected at eight standard time points during follow-up of 1 to 3 years, including clinical symptoms and signs, nerve conduction studies (NCS), biomaterial (serum and cerebrospinal fluid) and outcome assessments.

Results:
IGOS has included the aimed 2000 patients between April 2012 and May 2021. The last included patients are still in follow-up (until May 2024). Patients with alternative diagnoses (n=109, 5%), insufficient data (n=12, <1%) or protocol violations (n=43, 2%) are excluded. Sensorimotor GBS is reported in 1081 (59%) patients, pure motor in 405 (22%), pure sensory in 24 (1%), Miller Fisher and Miller Fisher-overlap in 212 (12%), ataxic form in 29 (2%), other variants in 45 (2%) and is missing in 46 (2%). Samples from entry or week 1 are available for 1510 (82%) patients which were all tested for five infections previously associated with GBS (*Campylobacter jejuni*, *Mycoplasma pneumoniae*, hepatitis E virus, cytomegalovirus and Epstein-Barr virus) and for IgM, IgG and IgA antibodies to 136 (combinations of) glycolipids in glyco-arrays. Genome-Wide Association Studies with samples from the first 1000 patients are ongoing. Several comparative treatment studies are in preparation.

Conclusions:
At the PNS meeting we will provide an update on the two-year follow-up of the cohort and all research projects ongoing in IGOS.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Guillain-Barré Syndrome, neuropathy, IGOS

Machine Learning Techniques To Improve Existing Prognostic Models For The Guillain-Barré Syndrome

Poster No:
P 365

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Introduction:
Machine learning techniques are increasingly used in the development of prognostic models for diseases, especially when using extensive and complex databases. The modified Erasmus GBS Outcome Score (mEGOS) is an existing prognostic model based on 3 clinical characteristics that predicts the inability to walk 10 meters unaided during follow-up of 26 weeks in patients with Guillain-Barré Syndrome (GBS). This model has recently been validated in the International GBS Outcome Study (IGOS), a prospective observational cohort study on the disease course of GBS. In a new project, machine learning techniques are used to investigate if the accuracy of the mEGOS can be improved.

Methods:
Clinical data from IGOS and IGOS Zika were used to predict the inability to walk at week 26, with data from standard time points at study entry and week 1. Variables with more than 10% missing data were not used in the analysis. Remaining missing data were imputed using the k-Nearest Neighbor algorithm. Clinical features with distinct distributions across classes (Jensen-Shannon divergence ≥ 0.1) were used to train the models. Classification algorithms were trained using 10-fold cross-validation, and performance was evaluated using sensitivity/specificity and the Matthews Correlation Coefficient (MCC).

Results:
IGOS has included 2000 patients and IGOS Zika 49 patients. Of these patients, 165 (8%) were excluded because of other diagnoses or protocol violations and 276 (15%) were excluded from this analysis because of insufficient data, resulting in a dataset with 1615 patients. The features with the highest importance in multiple trained models included age, Medical Research Council (MRC) sum scores and GBS disability scale at used time points, and the number of days between onset of weakness and hospital admission.

Conclusions:
At the PNS meeting we expect to be able to present the first prognostic models based on machine learning techniques and their performance compared to the existing model.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Guillain-Barré Syndrome, IGOS, machine learning

Clinical criteria for CIDP variants: comparing the EAN/PNS with the ENFS/PNS criteria

Poster No:
P 366

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Introduction:
There are different criteria for the diagnosis of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) in the literature. This led to conflicting results across studies on their frequency, clinical presentation, outcome, and treatment response.

Methods:
We compared the clinical criteria for CIDP variants of the 2021 EAN/PNS guidelines with the criteria for atypical CIDP of the 2010 EFNS/PNS guidelines in 319 patients included in the Italian CIDP database who fulfilled the EAN/PNS electrodiagnostic criteria for CIDP.

Results:
Compared to the EFNS/PNS criteria, EAN/PNS criteria increased the percentage of patients meeting the definition of CIDP variant from 21% to 36%. When compared to the corresponding typical CIDP group, the 2010 EFNS/PNS and 2021 EAN/PNS criteria identified equally distinct patient populations.

Multifocal, distal, and sensory CIDP were all characterized by milder impairment and symptoms. Additionally, multifocal CIDP displayed male predominance, lower rate of hyperproteinorrachia, and lower response to treatment and intravenous immunoglobulins. Distal CIDP patients were older at disease onset but showed similar response to treatment. Sensory CIDP patients were older at disease onset and presented lower rates of distal latency prolongation and reduced conduction velocity, but a higher rate of prolonged F-wave latency on nerve conduction studies. Motor CIDP was characterized by a relapsing-remitting history and higher rates of prolonged F-wave latency detection.

Conclusions:
The 2021 EAN/PNS clinical criteria enlarge the cohort of CIDP patients defined as variants but still identify distinct CIDP populations compared to the EFNS/PNS criteria. Since the EAN/PNS guidelines provide more definite criteria for the diagnosis of CIDP variants they better help to identify CIDP variants and should be used in future studies on patients with CIDP.

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No

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References 3:

References 4:

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Keywords: chronic inflammatory demyelinating polyradiculoneuropathy , CIDP Variants, Atypical CIDP, Lewis-Sumner syndrome, Distal Acquired Demyelinating Symmetric neuropathy

Anti-MAG IgG antibodies occur and matter in anti-MAG neuropathy

Poster No:
P 367

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Introduction:
Anti-MAG neuropathy is due to a monoclonal IgM gammopathy that targets the Human Natural Killer 1 (HNK-1) epitope bared by the myelin associated glycoprotein (MAG). In a previous study, we observed that anti-MAG IgG antibodies can also be detected in some patients. Our aim was to determine the frequency and specificity of these antibodies and whether they were associated with disease severity.

Methods:
Were included 46 anti-MAG neuropathies, 31 Chronic Inflammatory Demyelinating Polyradiculoneuropathies, 16 Multifocal Motor Neuropathies, 15 Multiple Sclerosis, 9 Charcot-Marie-Tooth neuropathies and 61 healthy controls. Disease severity was assessed trough muscle testing, sensory ataxia scoring, overall neuropathy limitation scale (ONLS), motor unit number index (MUNIX), and the sum of distal motor and sensory amplitudes.

Results:
Anti-MAG IgG antibodies were positive in 35/46 (76%) anti-MAG neuropathies versus none of the controls ($p<0.001$). These antibodies mainly recognised the HNK-1 epitope. Patients with positive anti-MAG IgG were more likely to have motor weakness or sensory ataxia (26 vs 2 patients, $p = 0.004$), worse ONLS leg score (2 vs 1, $p = 0.027$), lower MUNIX sum score (220 vs 240, $p= 0.014$), lower motor (21 vs 25 mV, $p = 0.001$) and sensory (7 vs 33 microV, $p = 0.007$) amplitudes sum scores. In-vitro competition between a polymer mimicking the HNK-1 epitope and anti-MAG IgG antibodies also correlated with patients 'disability scores.

Conclusions:
Anti-MAG IgG antibodies are specifically detected in some anti-MAG neuropathies characterised by a more severe disease. Further investigations are needed to understand the pathogenesis of these IgG antibodies.

References:
No

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References 2:

References 3:

References 4:

Grant Support:

Keywords: Anti-MAG neuropathy , anti-MAG IgG antibodies , HNK1

CIDP is part of the spectrum of VEXAS syndrome, therapeutic implications

Poster No:
P 368

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Introduction:
VEXAS (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) is an adult-onset syndrome caused by somatic mutations in UBA1 gene (ubiquitin-like modifier-activating enzyme 1) in hematopoietic progenitor cells. It associates myelodysplastic syndrome (MDS) and autoinflammatory diseases

Methods:
We report the association of VEXAS syndrome with 2 cases of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) and its therapeutic implication

Results:
A 74-yo man developed, in a few days, diffuse areflexia, muscle weakness and dysesthesia of the 4 limbs. Past medical history included MDS, polychondritis and pulmonary embolism. Electrodiagnosis (EDX) revealed a demyelinating neuropathy. Proteinorachia was slightly increased (0.81g/l). The patient dramatically improved after one course of intravenous immunoglobulins (IVIg), but he relapsed 3 months later and became bed-ridden. Nerve biopsy showed thin myelin sheaths and onion-bulb formations. A Met41Leu mutation was found in UBA1 gene. Association of steroids and Janus kinase treatments led to a sustained improvement with minimal impairment. A 69-year-old man complained of weight loss, recurrent fever, erythematopapular rash, orchitis, bilateral atrial chondritis, and episcleritis. He developed, in a couple of weeks, an asymmetric sensory and motor deficit of the 4 limbs. EDX showed conduction blocks on both median nerves and left ulnar nerve. Nerve biopsy excluded vasculitis and showed myelin alteration. Hematologic assessment identified a MDS. A Met41Thr mutation was found in UBA1 gene. IVIg were partially effective but were discontinued due to thromboembolic events. Six courses of azacitidine led to a dramatic improvement and complete remission of MDS and polychondritis. Improvement started after two courses of azacitidine and lasted three years without further treatment.

Conclusions:
Acute-onset and multifocal CIDP are part of the spectrum of the VEXAS syndrome. This diagnosis allows to use alternative treatments such as azacitidine or Janus kinase inhibitors in case of treatment-resistant CIDP.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: CIDP, VEXAS, Azacitidine, Janus kinase inhibitor

Effect of monovalency on anti-contactin-1 IgG4

Poster No:
P 369

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Introduction:
Autoimmune nodopathies (AN) have been diagnosed in a subset of patients fulfilling criteria for chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) who display no or poor response to intravenous immunoglobulins. Biomarkers of AN are autoantibodies, mainly IgG4, directed against the ternary paranodal complex composed by neurofascin-155, contactin-1 (CNTN1), and CASPR1. IgG4 can undergo a Fab-arm exchange (FAE) which results in functionally monovalent antibody. Here, we have evaluated the impact of valency on the action of anti-CNTN1 IgG4.

Methods:
Sera were obtained from 20 patients with AN associated with anti-CNTN1 antibodies. The proportion of monospecific/bispecific anti-CNTN1 antibodies was determined in each patient by ELISA. Anti-CNTN1 IgG4 were enzymatically digested into monovalent Fab using papain. The effects of native IgG4 and Fab fragments were tested on the interaction between Nfasc155 and CNTN1/CASPR1 in vitro using cell aggregation assay. To determine whether Fab may penetrate paranode, intraneural injections were performed, and antibody infiltration was monitored 1 and 3 days post injection.

Results:
We found that the percentage of monospecific antibodies were lower than 5% in 14 out of 20 patients (70%), suggesting that IgG4 have undergone extensive FAE in situ. The levels of monospecific antibodies correlated with the titers of anti-CNTN1 antibodies. However, patients with low or high percentage of monospecific antibodies similarly showed a severe phenotype. Native anti-CNTN1 IgG4 were shown to inhibit the interaction between cells expressing CNTN1/CASPR1 and cells expressing neurofascin-155 using an in vitro aggregation assay. Similarly, monovalent Fab significantly inhibited the interaction between CNTN1/CASPR1 and neurofascin-155. Both Fab and native anti-CNTN1 IgG4 potently penetrated the paranodal regions and completely invaded this region by day 3.

Conclusions:
These data indicate that monovalency does not affect the function blocking activity of anti-CNTN1 IgG4. This suggests that FAE may not impact the pathogenic potential of anti-CNTN1 IgG4 autoantibodies and could explain the severe clinical presentation in those patients.

References:
No

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References 3:

References 4:

Grant Support: Supported by the Agence Nationale pour la Recherche (NECCIN; GT and JJD), from the Association Française contre les Myopathies (grant#23593; GT and JJD), and by ArgenX.

Keywords: axon, node of Ranvier, CIDP, GBS, demyelination

Guillian Barre' Syndrome with treatment related fluctuations or CIDP: the clinical dilemma

Poster No:
P 370

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Introduction:
We present a case of acute onset CIDP presenting as GBS with treatment related fluctuation who had atypical features such as cranial nerve involvement, respiratory failure and prominent sensory ataxia.

Methods:
Case Report

Results:
27 year female presented with acute onset dysphagia, diplopia and difficulty walking that progressed to weakness in the upper extremities. Nerve conduction study revealed features of demyelination and cerebrospinal fluid was consistent with albuminocytogical dissociation. She was diagnosed as Guillian-Barre' Syndrome (GBS) and started on intravenous immunoglobulin (IVIG) 2g/kg divided over 5 days. However, weakness worsened and she was intubated for respiratory failure. A repeat course of IVIG was given. She remained on ventilator with a strength of grade 1 MRC. Dut to unresponsiveness to IVIG, she underwent plasmapheresis to which she responded dramatically and was extubated. After 4 days, strength in the upper extremities worsened. She underwent additional 2 sessions of plasmapheresis and was started on oral steroids with azathioprine. She improved slowly and was walking at 2 months. Azathioprine had to be stopped due to pancytopenia. Oral steroids were tapered off. A month later, she developed a relapse with diplopia and weakness in lower extremities that improved with plasmapheresis. She experienced a third relapse 2 months later with severe sensory ataxia. She improved with IVIG followed by injection rituximab 1000 mg 2 weeks apart. Anti-contactin and neurofascin antibodies were negative.

Conclusions:
This case highlights that if a patient with GBS has three or more fluctuations over > 8 weeks, it strongly suggests CIDP. Rarely acute-CIDP may present with prominent respiratory failure, cranial nerve involvement and sensory ataxia. A nodopathy needs to be considered in this scenario. Treatment with plasmapheresis may be carefully selected on a case by case basis if patient fails to respond to IVIG as in this case.

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Yes

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Grant Support:

Keywords: Guillian Barre' Syndrome , Treatment related fluctuations , CIDP , Sensory ataxia , intravenous immunoglobulin

A Single-Center Retrospective Chart Review Of The Diagnosis And Management Of Chronic Inflammatory Demyelinating Polyradiculoneuropathy

Poster No:
P 371

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Introduction:
Chronic inflammatory demyelinating polyradiculoneuropathy is often misdiagnosed. The diagnostic accuracy and management profile of an intra-departmental cohort of CIDP patients are reviewed. The use of immunosuppressant therapy for patients with presumed CIDP not meeting updated diagnostic criteria is characterized.

Methods:
A database of 158 patients with a chart-queried diagnosis from 2018 to 2021 was generated. CIDP diagnoses were re-evaluated with updated EAN/PNS guidelines (1). Patients without an electrodiagnostic study on institutional record were excluded. Patients were then categorized into revised diagnostic cohorts. Maintenance treatment regimens were characterized. Demographic comparisons utilized student's t-test and Chi-square tests.

Results:
After exclusion of patients without electrodiagnostic study, 134 patients remained. Of these patients, 34% met EAN/PNS criteria for Typical CIDP and 50% met a composite of Typical CIDP and Possible CIDP. Axonal neuropathies (12%), small fiber neuropathies (11%), anti-Nodal neuropathies (8%), and anti-MAG neuropathies (7%) were the most common diagnoses initially retrieved into the database as CIDP. The population demographics were not significantly different. 69% of composite CIDP patients received immunoglobulin therapy (IVIG or SCIG), 10% were on steroid monotherapy, and 9% were on alternate immunosuppressants. Notably, 73% of presumed inflammatory small fiber neuropathies and 94% of axonal neuropathies included in the initial CIDP diagnosis cohort were managed with immunoglobulin therapy for presumed autoimmune etiology.

Conclusions:
This study underlines the clinical challenge of accurate CIDP diagnosis and highlights the role for applying updated diagnostic criteria to suspected CIDP patients. The rate of alternate diagnoses initially characterized as CIDP is similar to that reported in prior literature (2). It also reveals a proportion of patients with chronic neuropathy initially characterized as CIDP but ultimately presumed to be inflammatory small fiber or axonal neuropathy who receive immunotherapy. This sub-population requires further study, as evidence is lacking regarding the efficacy of immunotherapy in this group (2,3).

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Yes

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Geerts M, de Greef BTA, Sopacua M, et al. Intravenous immunoglobulin therapy in patients with painful idiopathic small fiber neuropathy. Neurology. 2021;96(20):e2534-e2545.

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Grant Support:

Keywords: Chronic Inflammatory Demyelinating Polyradiculopathy, Inflammatory Neuropathy, Intravenous immunoglobulin

Skin Punch Biopsy Abnormalities Among Patients with IgM MGUS or Waldenström Macroglobulinemia and Peripheral Neuropathy

Poster No:
P 372

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Introduction:
Peripheral neuropathy is common among patients with IgM monoclonal gammopathy of undetermined significance (MGUS) or Waldenström macroglobulinemia (WM). A definitive link to the paraproteinemia remains uncertain in many patients, complicating treatment decisions. Establishing an etiology may be especially challenging in patients with axonal pathophysiology or normal findings on NCS/EMG. We aimed to reveal novel etiologic mechanisms of neuropathy among such patients by performing skin biopsies to evaluate for monoclonal protein deposition.

Methods:
136 patients (31 with IgM-MGUS, 105 with WM) with symptoms of neuropathy had three full-thickness skin punch biopsies: one specimen from the abdomen and two from the distal lower extremity. Biopsies were evaluated for the presence of monoclonal immunoglobulin, clonal light chains, and amyloid deposition via light microscopy, immunofluorescence microscopy, and electron microscopy. Pathologic findings were correlated with clinical and electrodiagnostic characteristics.

Results:
Biopsies from 53 patients (39%) demonstrated abnormalities of varying patterns. 47 patients had monoclonal IgM (mIgM) deposition in dermal nerves (27), microvasculature (17), and/or the dermis (12). Immunoglobulin-storing histiocytosis was seen in two of these. Patients with mIgM deposition had higher serum IgM levels than those with negative biopsies ($p<0.01$). Otherwise, five patients had findings consistent with amyloidosis, of which four had no prior pathologic evidence. One patient had focal peri-vascular and glandular infiltration of lymphoplasmacytic cells. 21 of the patients with abnormal biopsies had no evidence of large-fiber neuropathy on NCS/EMG. 9 of 24 patients with both anti-MAG antibodies and demyelinating features on NCS/EMG had findings of mIgM deposition.

Conclusions:
In conclusion, further investigation is warranted to determine whether these pathologic findings of mIgM deposition in skin, nerves, and vasculature could help inform the care of patients with IgM paraproteinemia and neuropathy. In particular, the findings of an IgM-mediated vasculopathy are novel and could suggest an undescribed mechanism by which IgM paraproteinemia may lead to neuropathy.

References:
No

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Grant Support:

Keywords: Paraproteinemic Neuropathy, Waldenstrom Macroglobulinemia, Anti-MAG Neuropathy, Amyloidosis, IgM Neuropathy

GUILLAIN-BARRE SYNDROME AND PULMONARY EMBOLISM IN AN ADULT FEMALE WITH COVID-19 INFECTION IN GHANA.

Poster No:
P 373

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Introduction:
The coronavirus disease 2019 (COVID-19) pandemic began at the end of 2019. This novel coronavirus was classified as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Guillain-Barré syndrome (GBS) is the commonest acute post-infectious neuropathy. A number of case reports have described GBS occurring soon after COVID-19 infection, but to date this link remains unproven. On the other hand, the predisposition to thromboembolism is well established in COVID-19. We present a case of GBS and pulmonary embolism temporally related to COVID-19 infection in Ghana, West Africa.

Methods:
A 60-year-old, apparently healthy female, was referred to the COVID-19 treatment centre from a referral centre for low-grade fever, chills, rhinorrhoea, and generalised flaccid limb weakness for a week.

Results:
A positive SARS-CoV-2 test had been recorded 3 days after the onset of symptoms. Clinical examination revealed, no cranial nerve palsies with symmetric areflexic flaccid paraparesis. This rendered the patient bedridden needing constant nursing care. Following cerebrospinal fluid (CSF) analysis, neurophysiological studies and a chest computed tomography pulmonary angiogram, Guillain-Barre syndrome and pulmonary embolism were confirmed. She was started on anticoagulants; but for GBS she was only managed supportively as IVIG and plasma exchange are costly and not easily available in Ghana. After 10 days, she started making modest improvement in limb power and function.

Conclusions:
This case highlights the need to anticipate potential thromboembolic complications such as deep venous thrombosis and pulmonary embolism in patients with COVID-19, especially if they have a co-existing paralytic disorder like GBS. The association of GBS with COVID-19 requires further prospective and case-controlled studies. These are being systematically planned in the country.

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Abu-Rumeileh, S., et al., Guillain-Barré syndrome spectrum associated with COVID-19: an upto-date systematic review of 73 cases. Journal of neurology, 2020: p. 1-38.

Grant Support: None

Keywords: Guillain-Barre syndrome, Pulmonary Embolism, Neuropathy

Characterization of neuroinflammation in a mouse model of chronic neuritis

Poster No:
P 375

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Introduction:
Chronic inflammatory demyelinating polyneuropathy (CIDP) is one of the most common autoimmune diseases of the peripheral nervous system (PNS) and presents as clinically heterogeneous disease affecting the peripheral nerves and nerve roots. Pathological features include inflammatory infiltrates, segmental demyelination, and axonal degeneration. The ICAM-1-deficient NOD mouse represents a spontaneous model of chronic neuritis that shares several pathological features with CIDP, including responsiveness to IVIg. Here, we aimed to further characterize the extent of neuroinflammation and neurodegeneration at different time points of disease progression in the sciatic nerves of female NOD ICAM-1-deficient mice.

Methods:
We employed immunohistochemistry to investigate key immune cell populations including T-lymphocytes (CD3, CD4, CD8), B-lymphocytes (B220) and macrophages (CD11b) by means of quantity and localization. In addition, dedifferentiating Schwann cells (Sox2) were analyzed. Moreover, extensive morphometric assessment was performed.

Results:
Evaluation of immunohistochemistry showed that disease severity correlated with cell infiltration of T-cells, B-cells, macrophages, and upregulation of the dedifferentiation marker Sox2 in Schwann cells. Most cell infiltrates were randomly distributed throughout the nerve, with some cell accumulation in the proximal nerve root region. In addition, it was shown that CD4+ and CD8+ T cells infiltrate the nerve at equal proportions, indicating a shift in the CD4/CD8 ratio. Morphometric analyses indicated that the extent of axonal loss strongly correlated with disease severity. While myelin thickness as determined by g-ratio measurements remained largely unaffected, we observed formation of 'onion bulb'-like structures.

Conclusions:
In conclusion, a strong correlation between disease severity, immune cell infiltration, Schwann cell dedifferentiation and nerve damage could be found, marking the NOD-ICAM1-deficient mouse as a valuable model for CIDP.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: CIDP, inflammatory neuropathy, NOD ICAM-deficient, Schwann cell, Morphometry

Monomelic Brachial Plexus Neuropathy: An Uncommon Presentation Of Focal Chronic Inflammotory Demeylinating Polyradiculoneuropathy

Poster No:
P 376

Authors:
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Institutions:
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Introduction:
A 24-year-old lady with progressive without fluctuations one year course of weakness and wasting of right upper limb. She frequently complains of increase sensation to temperature in that limb.

Methods:
Examination revealed weakness in flexors and extensors of elbow, wrist and all finger movements with wasting involving small muscles of hand and forearm. Absent biceps, brachioradialis and triceps reflexes. Abnormal sensation in digits V, IV and III; milder numbness in digits II, and lateral and medial forearm. No Horner's syndrome. Hyperthesia to hot and cold objects in right upper limb. Subtle weakness of UMN nature in right lower limb.

Results:
Motor NCS of right upper limb showing extremely low to absent CMAPs and SNAPs in all examined proximal and distal nerves with EMG picture of neuropathic motor units with fibrillations and positive sharp waves at rest. Routine lab was normal. CSF analysis showed elevated protein content. Magnetic resonance imaging of the brachial plexus revealed remarkable fusiform thickening and enhancement of the right sided C7 and C8 exiting nerve roots, the middle and lower trunk of the brachial plexus and to a lesser degree their divisions and distal cords with increased signal in T2 weighted and short tau inversion recovery images, no evidence of root avulsion and preserved preganglionic rootlet, no masses or vascular abnormalities at the root of the neck or thoracic outlet.

Conclusions:
Based on previous findings a possible diagnosis of focal CIDP variant was established and the patient started a course of repeated monthly pulse therapy of intravenous methylprednisolone with good clinical improvement regarding her sensory symptoms. Atypical CIDP variants differ not just in their clinical and electrophysiological characteristics but also in their response to conventional immunosuppressive therapy effective against typical CIDP. Potential biomarkers and diagnostic criteria are still lacking.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: CIDP, neuropathy, plexus, focal , atypical

Mycophenolate facilitates IVIg reduction in CID

Poster No:
P 377

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Introduction:
Background: Intravenous immunoglobulin (IVIG) is an effective first line treatment in CIDP but a small proportion of responders require ultra-high dose (>2g/kg/month) or co-prescription of corticosteroids to maintain adequate clinical response. There is limited evidence for the role of mycophenolate in this patient sub-set. Aims: To assess the effectiveness of mycophenolate on patient outcome, IVIg dose and cost in a cohort of CIDP patients requiring ultra-high dose IVIg maintenance

Methods:
Methods/Materials: Retrospective case note review of patients treated with MMF after being established on IVIG therapy for CIDP from the NHNN inflammatory neuropathy cohort. We recorded IVIg dose and regimen, and clinical outcome measurements (CIDP-RODS, MRC-SS) before introduction of MMF and at 6 months after maximum MMF dose was reached. Statistical analysis was performed in Microsoft Excel.

Results:
Results: Eleven patients with CIDP (1/11 NF155 antibody positive, 1/11 motor variant) were included. 8/11 male, mean age 54.5 (s.d 15.5) years, mean duration of disease was 5 (s.d. 3.4) years. Mean duration of mycophenolate treatment was 17.2 (s.d. 20.5) months, with a mean dose of 2.8 (s.d. 0.4)g daily. MMF therapy was well tolerated by all patients. At latest follow up there was a mean IVIg dose reduction of 0.7g/kg/month, mean reduction in day care attendance of 1.5 days/month. Median I-RODS improved from 24/48 to 39/48, with an improvement in median MRCSS from 58/70 to 69/70. Overall, this has a total IVIg saving of 4137 grams over 6 months within our cohort of patients. The estimated savings for the IVIG were £165,514 in over 6 months.

Conclusions:
Conclusion: Mycophenolate is a well-tolerated alternative and /or IvIg 'sparing agent' for maintenance therapy in CIDP with positive impact on IVIg dose and cost alongside improvement in clinical outcome measurements. A formal randomized controlled trial is required.

References:
Yes

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References 3:
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References 4:
Van den Bergh PYK, van Doorn PA, Hadden RDM, Avau B, Vankrunkelsven P, Allen JA, Attarian S, Blomkwist-Markens PH, Cornblath DR, Eftimov F, Goedee HS, Harbo T, Kuwabara S, Lewis RA, Lunn MP, Nobile-Orazio E, Querol L, Rajabally YA, Sommer C, Topaloglu HA.

Grant Support: nil

Keywords: CIDP, mycophenolate, chronic inflammatory demyelinating neuropathy, I-RODS, MRCSS

A Multi-Centre Retrospective Cohort Study of Dysautonomia Monitoring in Guillain-Barré Syndrome

Poster No:
P 378

Authors:
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Introduction:
Guillain-Barré Syndrome (GBS) is an inflammatory polyradiculoneuropathy with varying phenotypes that can include any combination of sensory, motor and autonomic nerve dysfunction. Dysautonomia occurs in around 60% and can manifest as heart rate and blood pressure abnormalities, pupil abnormalities, paralytic ileus and urinary retention. Evidence for dysautonomia monitoring requirements in GBS is lacking even though life threatening dysrhythmias can occur in rare cases.

Methods:
We performed a retrospective cohort study of incident GBS at 4 UK Centres between December 2019 and October 2022. Patients were identified through intravenous immunoglobulin (IVIg) databases and/or local medical record search. Published criteria were used to verify diagnosis and identify autonomic dysfunction. Data was collected from observation charting and medical records.

Results:
47 patients were included, mean age 54.3 years (SD 15.91), 64% female. 56% AIDP, 26% AMSAN/AMAN, or GBS variant (Fisher syndrome, ataxic). Median day 7 mEGOS score was 4.8 (SD 3.4), mean length of stay 32.5 days (SD 25.7). 33% required ITU care, 22% invasive ventilation. 45 patients (95%) had at least one feature of dysautonomia. Medical recognition of dysautonomia was variable with more patients screened for gastrointestinal (95%), urinary (68%) and pupillary (72%) abnormalities, but only 32% had postural BP measurements, 33% a baseline electrocardiogram, and 46% continuous cardiac monitoring. There were discrepancies between observations meeting criteria for cardiovascular dysautonomia and its medical documentation: only 5/36 cases with labile BP, 15/28 with persistent tachy- or bradycardia, 12/18 with persistent hypertension.

Conclusions:
Dysautonomia is common, with variable manifestations in GBS. This study suggests medical awareness is sub-optimal. Improving dysautonomia care could impact patient experience and, in rare cases, save lives.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Guillain-Barré Syndrome (GBS), Dysautonomia, Monitoring

A GUILLAIN-BARRE SYNDROME NATIONWIDE SPANISH EPIDEMIOLOGICAL STUDY IN THE COVID YEARS

Poster No:
P 379

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Introduction:
Guillain Barre syndrome (GBS) is an acute immune-mediated polyradiculopathy, with a variable incidence described around the world, from 0.44 per 100,000 inhabitants in Japan to 2.2 in the US (1). The epidemiology in Spain was described by Cuadrado et al (2) in the 1990s and other studies showed the epidemiological characteristics of specific areas of the country (3,4). However, this is the first nationwide study, including data from all public hospitals in the country and addressing variability across different regions.

Methods:
Observational study based on hospital database collected by the Specialized Healthcare Registry (RAE-CMBD) - Spanish Ministry of Health, including a minimal dataset of all specialized public and private Healthcare Centers in Spain. Patients discharged with GBS as the main diagnosis and admitted during 2018-2020 were included. In-hospital incidence rates were estimated based on the mid-year population registered in the National Statistics Institute (INE) for each year.

Results:
In total, 2363 cases were included, 832 in 2018, 861 in 2019 and 670 in 2020. The mean age was 53.2 years (SD 21.9) with 64.3% male. The hospital incidence (cases/100,000 population) nationwide was 1.78 in 2018, 1.83 in 2019 and 1.41 in 2020, with an increased frequency of cases in the winter season and in the over-65 age group. No correlation between COVID and GBS incidences was observed in the year 2020.

Conclusions:
In our country, the incidence of GBS is somewhat higher than that described in previous studies, probably in relation to the aging of the population. Unlike descriptions in previous reports, a decrease of GBS incidence during the SARS-CoV-2 pandemic was observed. We expect to have updated data from 2021 to analyze GBS incidence in relationship with SARS-COV2 vaccination. Final results will be presented at the congress.

References:
Yes

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References 2:

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Grant Support:

Keywords: inflammatory, neuropathy, Guillain Barre Syndrome, Epidemiology

Systematic analysis of serum neurofilament light chain levels in the CIDP01/CIDP04 clinical trials

Poster No:
P 380

Authors:
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Introduction:
Serum neurofilament light chain (sNfL) is, so far, the best biomarker to detect axonal damage in peripheral neuropathies. For this reason, it is included in the biosampling protocols of peripheral neuropathy clinical trials, including chronic inflammatory demyelinating polyneuropathy (CIDP). Most studies perform a simple comparison of total sNfL values across trial arms or use an arbitrary cut-off level in the analysis. The aim of this study is to report a detailed analysis of sNfL levels in serum samples from the patients included in the CIDP01/CIDP04 clinical trials assessing the safety and efficacy of rozanolixizumab, a neonatal Fc receptor (FcRnN) inhibitor, compared to placebo in patients with CIDP.

Methods:
We measured sNfL levels using single molecule array (SIMOA®) assay in serum samples from 34 patients with CIDP included in CIDP01/04 clinical trials and 49 healthy controls (HC). Levels were described according to age and body mass index-adjusted percentiles and z-scores. Comparisons were performed between treatment and placebo groups, occurrence of relapse during the trial period, presence of known autoantibodies and reactivity against neural tissues.

Results:
CIDP patients had significantly higher sNfL than age-matched HC (13pg/ml vs 7.9pg/ml, p=0.005). No differences were found between treatment and placebo groups at baseline or follow-up. Patients with known autoantibodies had a higher median sNfL value that was not statistically significant (20 vs 13pg/ml, p=0.27). Patients reacting against monkey peripheral nerve tissue had higher final sNfL levels (28 vs 12pg/ml, p=0.03).

Conclusions:
No differences in sNfL levels were found between rozanolixizumab and placebo groups, in agreement with the negative results from the study. Taking baseline sNfL levels as a biomarker of ongoing axonal damage in addition to autoantibody profiles prior to clinical trial inclusion could help optimizing patient selection in future CIDP trials. A protocolized and systematic analysis of sNfL levels at specific timepoints may be useful for comparative studies in CIDP.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: neurofilament light chain, rozanolixizumab, chronic inflammatory demyelinating polyneuropathy, neonatal Fc receptor

Brain-derived tau and big-tau levels in peripheral neuropathies

Poster No:
P 381

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Introduction:
Biomarkers for monitoring disease activity and treatment outcomes in patients with neuropathies are lacking. Recently, serum neurofilament light chain (sNfL) concentration was associated with disease severity in some neuropathies, but it is a general marker of neurodegeneration and it is not nerve-specific. A high-molecular-weight isoform of tau protein, called big-tau, is predominantly expressed in PNS. Our objective is to study big-tau and brain-derived tau (BD-tau) in patients with neuropathies and compare them with CNS diseases.

Methods:
Ultra-sensitive blood-based assays developed at the University of Gothenburg and ran on an HD-X Single molecule array analyser were used to measure big-tau and BD-tau concentrations in serum samples from 89 Guillain-Barré syndrome (GBS) patients, included in the IGOS study in Spain, 102 Charcot-Marie-Tooth (CMT) patients, 43 chronic inflammatory demyelinating polyneuropathy (CIDP) patients and 160 multiple sclerosis (MS) patients. Results were compared with sNfL analysis previously performed in GBS patients.

Results:
GBS patients had significantly higher BD-tau levels than CIDP (3.13 vs 2.29pg/ml, p=0.02) and MS patients (1.7pg/ml, p<0.001), but similar levels to CMT patients (3.68pg/ml). GBS patients had significantly higher big-tau levels than MS patients (11.25 vs 9.03pg/ml, p=0.01) but similar levels to CIDP or CMT patients (10.07 and 9.87pg/ml, respectively). No differences were found between axonal and demyelinating variants in GBS or CMT patients. Miller-Fisher syndrome had lower big-tau/BD-tau ratio than other GBS variants (1.27 vs 3.27, p=0.04). GBS patients with ganglioside antibodies had higher

levels of both biomarkers. BD-tau and big-tau correlated with clinical scales at the beginning of the disease in GBS patients (MRC at 1 week and I-RODS at 4 weeks). Unlike sNfL levels, neither tau biomarkers showed long-term clinical correlations.

Conclusions:
BD-tau and big-tau correlated with clinical scales early in the disease in GBS patients, but both had a weaker correlation than sNfL levels. Final results will be presented at the congress.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: tau, biomarkers, peripheral neuropathies

Polyneuropathies Without A Cause; A Survey of Clinical Practice

Poster No:
P 382

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Introduction:
Polyneuropathy is a heterogeneous disease with many causes, and the etiological diagnostic process is often complex and time-consuming. A stepwise systematic approach based on clinical classification has been recommended for the past two decades. Our aim was to examine the quality of polyneuropathy work-up in a general Department of Neurology by charting the proportion of polyneuropathies ending up with an identified cause and whether the presumed idiopathic polyneuropathies are investigated according to clinical phenotype and evidence based recommendations.

Methods:
Medical records of patients diagnosed with chronic polyneuropathy at a Department of Neurology in the period from 2010 to 2017 were reviewed.

Results:
A total of 226 patients diagnosed with chronic polyneuropathy were identified and 60 of them where considered idiopathic. The medical records of the presumed idiopathic polyneuropathies had insufficient description of family history in 60%, distribution and description of motor or sensory involvement in 55%, disease time course in 30%, medical history in 10%, alcohol consumption in 43%, and other toxin exposure in 98% of the cases. Complete recommended blood test screening lacked in 17%. Thirty-eight % of the patients fulfilled the criteria for chronic idiopathic axonal polyneuropathy retrospectively, but this term was seldom used in the medical records. Twenty-seven % of the presumed idiopathic polyneuropathies showed demyelinating features on nerve conduction studies, of which 50% lacked description of family history and 44% lacked cerebrospinal fluid exam in their work-up.

Conclusions:
The proportion of idiopathic polyneuropathies was in accordance with international epidemiological studies. However, based on medical records, the diagnostic approach to identify underlying cause was partially deficient and unsystematically performed. More use of clinical classification will probably improve the diagnostics of polyneuropathies.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: polyneuropathy, CIAP, work-up, clinical classification, phenotype

Seasonal Variation in Occurrence of Guillian Barre Syndrome (GBS) in Our Local Population

Poster No:
P 383

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Introduction:
Guillian Barre Syndrome(GBS) is an acute acquired, immune-mediated polyradicular neuropathy and is one of the most common cause of acute flaccid paralysis with potential of life threatening complications. Although there has been reports of seasonal variations in occurrence of GBS but no confirmed constant seasonal variations is yet known.

Methods:
This is retrospective cross-sectional study carried out at Neurology Department in collaboration with various private and public hospitals in Punjab.The study period was two years from March 2019 till February 2021.The patients fullfilling the Ashbury and Cornblath criteria for GBS and those who required plasmapharesis were included in the study. Exclusion criteria included patients of neuropathies associated with chronic inflammatory demyelination,diabetes ,other metabolic,toxic and vasculitic neuropathies. A proforma containing demographic,clinical, CSF findings and electrophysiological detail was designed which was filled by treating physician before requesting for plasmapheresis.The data was analyzed using SPSS version 16 and significant was determined by using Pearson's chi square test.

Results:
A total of 185 patients were included in the study with 112(60.5%)males and 73(39.5%) females and M:F ratio of 1.53: 1.The mean age was 35.24(SD 15.51) with range from 11-78 years. Ninety nine(53.5%) cases presented between 20- 40 years of age.The highest incidence of GBS (n=86, 46.5%) were seen in winter season (Dec-Feb),followed by 36(19.5%) in spring(March-May), 46(24.9%) in rainy summer(June-Sept) or southwest monsoon period and 17(9.2%) in post monsoon(Oct-Nov).This seasonal occurrence was significant(p=.ooo).

Conclusions:
Our study showed that there is significant (p=.000) variation in frequency of GBS patients with a clear predilection towards winter season.GBS is more common in males than females in our local population with maximum frequency between 20- 40 years of age.Largest studies are required to confirm our findings and possible association with upper respiratory tract infections such as influenza which are common during this season so that preventive measures can be taken to prevent this illness.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: GBS Guillian Barre Syndrome

Unclassified Clinical Presentations of Chronic Inflammatory Demyelinating Polyradiculoneuropathy.

Poster No:
P 384

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Introduction:
To assess the ability of the EAN/PNS clinical criteria for chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) to include within their classification the whole spectrum of clinical heterogeneity of the disease and to define the clinical characteristics of the unclassifiable clinical forms

Methods:

The EAN/PNS clinical criteria for CIDP were applied to 329 patients fulfilling the electrodiagnostic and supportive criteria for the diagnosis of CIDP. Clinical characteristics were reviewed for each patient not strictly fulfilling the clinical criteria ('unclassifiable').

Results:
At study inclusion, 124 (37.5%) patients had an unclassifiable clinical presentation, including 110 (89%) with a typical CIDP-like clinical phenotype in whom some segments of the four limbs were unaffected by weakness ('incomplete typical CIDP'), 10 (8%) with a mild distal, symmetric, sensory or sensorimotor polyneuropathy confined to the lower limbs with cranial nerve involvement ('cranial nerve predominant CIDP'), and 4 (1%) with a symmetric sensorimotor polyneuropathy limited to the proximal and distal areas of the lower limbs ('paraparetic CIDP'). Eighty-one (65%) patients maintained an unclassifiable presentation during the entire disease follow-up while 13 patients progressed to typical CIDP. Patients with the unclassifiable clinical forms compared to patients with typical CIDP had a milder form of CIDP, while there was no difference in the distribution patterns of demyelination.

Conclusions:
A proportion of patients with CIDP do not strictly fulfill the EAN/PNS clinical criteria for diagnosis. These unclassifiable clinical phenotypes may pose diagnostic challenges and thus deserve more attention in clinical practice and research

References:
No

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References 3:

References 4:

Grant Support:

Keywords: chronic inflammatory demyelinating polyradiculoneuropathy, diagnostic criteria, CIDP, diagnosis, guidelines

Risk of Disease Relapse, Safety and Tolerability of SARS-CoV-2 Vaccination in Patients with Chronic Inflammatory Neuropathies. The INCLUSIVE Study

Poster No:
P 385

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Introduction:
To evaluate the risk of relapse after SARS-CoV-2 vaccination, and its safety and tolerability, in chronic inflammatory neuropathies patients.

Methods:
We conducted a multicenter, cohort, and case-crossover study, from January 2021 to December 2021. Patients with a diagnosis of CIDP or MMN fulfilling the EFNS/PNS criteria for probable/definite

diagnosis whose dose and frequency of maintenance therapy had not been reduced in the previous three months or were in remission without ongoing active treatment were invited to participate. The risk of relapse associated with SARS-CoV-2 vaccination was assessed by comparing frequency of relapse in patients who underwent or did not undergo vaccination. Frequency of relapse in the three months prior and after vaccination, and safety and tolerability of SARS-CoV-2 vaccination were also assessed. Patients were objectively evaluated and completed a questionnaire at different time points.

Results:
336 patients were included (278 CIDP; 58 MMN). 307 (91%) patients underwent SARS-CoV-2 vaccination, including 269 (88%) with BNT-162b2-Pfizer/BioNTech, 28 (9%) with mRNA-1273-Moderna, and 10 (3%) with ChAdOx1-AstraZeneca. Twenty-nine patients (9%) did not undergo vaccination. Clinical relapse was observed in 16 (5%) patients (13 CIDP; 3 MMN) after SARS-CoV-2 vaccination and in none of the patients who did not undergo vaccination (RR= 3.21, 95% CI, 0.19-52.25). There was no increase in the specific risk of relapse associated with type of vaccine or diagnosis. Comparison with the 3-month control period preceding vaccination revealed an increased risk of relapse after vaccination (RR= 4.00; 95% CI, 1.35-11.82), which was restricted to CIDP patients (RR= 3.25, 95% CI, 1.07-9.84). The safety profile of SARS-CoV-2 vaccination was characterized by short-term, mild-to-moderate local and systemic adverse events.

Conclusions:
SARS-CoV-2 vaccination in CIDP patients seems to be associated with a small increased risk of relapse and with an acceptable short-term safety profile. The benefits of SARS-CoV-2 vaccination in CIDP and MMN patients outweigh the risk of disease relapse.

References:
No

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Grant Support:

Keywords: SARS-CoV-2, vaccination, CIDP, MMN

Prevalence and Characteristics of Peripheral Neuropathy in Patients with Psoriasis and Psoriatic Arthritis

Poster No:
P 386

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Introduction:
Different laboratory and clinical data suggest a link between neurogenic inflammation and pathogenesis of psoriasis. There are also anecdotal reports of peripheral neuropathy in patients with psoriasis. To assess the prevalence and clinical features of peripheral neuropathy in patients with psoriasis and psoriatic arthritis

Methods:
Patients with psoriasis or psoriatic arthritis (n=100) control subjects (n=100) were consecutively enrolled. Clinical neuropathy was diagnosed when symptoms and signs of peripheral sensory or motor involvement were present. Nerve conduction study was performed to confirm the diagnosis. Patients with a confirmed peripheral neuropathy also underwent laboratory and nerve ultrasound investigations.

Results:
One hundred patients with psoriasis or psoriatic arthritis and 81 controls were enrolled so far. Polyneuropathy was found in 9 (9%) patients (4 with psoriasis, 5 with psoriatic arthritis) and in none controls (p= 0.0056). Polyneuropathy was axonal, length-dependent, symmetric, sensory or sensorimotor in all patients. Polyneuropathy was significantly prevalent in both patients with psoriasis and psoriatic arthritis (p=0.0016 and p=0.0004, respectively). When excluding patients with an alternative cause for the polyneuropathy (2 with diabetes mellitus, 3 treated with TNFα inhibitors and 1 with isoniazid), the frequency of polyneuropathy in patients with psoriasis or psoriatic arthritis still remained significantly increased (p=0.045). In multivariate analysis, none of the factor examined (comorbidities, disease duration, medications) were significantly associated with an increased risk of polyneuropathy. Frequency of carpal tunnel syndrome did not differ between patients with psoriasis or psoriatic arthritis and controls.

Conclusions:
Preliminary results of our study show that psoriasis and psoriatic arthritis are associated with an increased risk of polyneuropathy. The risk seems to be partly secondary to the comorbidities frequently encountered in psoriasis and psoriatic arthritis and partly attributable to direct mechanisms.

References:
No

References 1:

References 2:

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Grant Support:

Keywords: psoriasis , psoriatic arthritis , polyneuropathy, carpal tunnel syndrome, neuropathy

Fine Specificity Of A Recombinant Anti-GM1 Antibody Derived From A Patient With GBS

Poster No:
P 387

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Introduction:
Anti-ganglioside antibodies play an important role in the pathophysiology of Guillain-Barré syndrome (GBS) through their pathogenic effects on peripheral nerves. Which antibody properties determine the pathogenic potential and whether these can explain the heterogeneity in clinical course and outcome remains unknown. To determine fine specificities and affinities of human anti-ganglioside antibodies, Campylobacter jejuni-specific plasmablasts from two GBS patients were isolated and recombinant IgG monoclonal antibodies (rIgG) were generated.

Methods:
Binding of rIgG and corresponding patient serum to gangliosides, glycolipid complexes, C. jejuni lipooligosaccharide (LOS) molecules, whole bacteria and oligosaccharide moieties of LOS and gangliosides was assessed by ELISA, glycoarray and microarray. Soluble antigen-binding inhibitory assays were used to assess binding affinity. Murine triangularis sterni preparations were used to assess ex vivo binding to peripheral nerve tissue.

Results:
One rIgG was generated that bound to GM1, GM1 complexes and sulfatide. Serum antibodies more broadly recognized GM1, GD1b, GA1 and corresponding complexes. Binding of both rIgG and serum IgG to GM1 was enhanced by the presence of sulfatide. The rIgG showed reactivity against GM1-mimicking LOS and whole C. jejuni bacteria with GM1-mimicking LOS, which was sialic acid-dependent. Both rIgG and serum showed a higher binding affinity for the patient-derived C. jejuni LOS with a GM1 mimic than for GM1. Incubation of triangularis sterni preparations with a high concentration of rIgG resulted in deposits of rIgG at the nodal gap and along myelin sheaths. Staining remained present in tissue lacking GM1 but was enhanced in tissue lacking sulfatides.

Conclusions:
For the first time, an anti-GM1 IgG antibody was cloned from a patient with GBS. The antibody bound with higher affinity to C. jejuni LOS as compared to GM1. Differential binding of the rIgG to GM1 in presence or absence of sulfatide further indicates that the local lipid environment influences antibody binding.

References:

No

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Grant Support:

Keywords: Guillain-Barré syndrome, Recombinant antibodies, Pathogenicity, Gangliosides, Campylobacter jejuni

Gut-Microbiota Dysbiosis in Treated and Supportively-cared Patients with Guillain-Barré Syndrome

Poster No:
P 388

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Introduction:
Guillain-Barré syndrome (GBS) is a post-infectious autoimmune disease with a marked variation in pathology, clinical presentation and prognosis. Gut-microbiota dysbiosis exerts a strong influence in host-immunity and can affect the clinical phenotype of GBS. We investigated the impact of gut-microbial diversity in association with clinical features to find out the role of gut-microbiota in treated and supportively-cared patients with GBS.

Methods:
We investigated 16s rRNA-gene [V4-region (515F-806R)] sequences of 158 fecal specimens collected from 60 patients with GBS at entry before treatment (n=60; 21 IVIg-treated, 18 PE & 21 supportive-care) and 6 months (n=40) with 58 age-sex/ethnicity-matched controls from Bangladesh. Sequence-data was analyzed using Qiime2-Dada2 pipeline. Differential relative abundance (RA) was calculated using LEfSe [LDA(Log10)].

Results:
Gut-microbial diversity differs significantly between patients with GBS before and after treatment with respect to control in pairwise permanova (beta diversity) and kruskal-wallis (alpha diversity) tests ($p=<0.05$). Genus Senegalimassilia was differentially abundant in GBS compared to controls and 6-month samples (LDA-score>3.0). However, after 6 months, patient showed differential relative abundance of Enterococcus (LDA-score>4.0) and Parabacteroids (LDA-score>4.0). Considering community richness, evenness and dissimilarity; gut microbiota differs significantly in patients with good outcome compared to poor outcome after treatment with IVIg or PE at 6-months ($p<0.05$). On the basis of subgroups for requirement of ventilation, dysautonomia, severity and death status, alpha and phylogeny-based beta diversity were different ($p<0.05$). Linear discriminant analysis effect size determined that Escherichia_Shigella and Family_XIII_AD3011 genera were differentially abundant (LDA-Score>4.0) in patients who have died due to complication in GBS.

Conclusions:
Gut-microbiota altered in GBS with severity, in response to treatments and mortality. Differentially abundant taxa may help tracking treatment response as well as to predict possible worst consequence of GBS. Meta-trancriptomic gene expression level analysis may contribute to elucidate the function of differentially abundant organisms.

References:
No

References 1:

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References 3:

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Keywords: Guillain-Barré syndrome, Gut-microbiota , 16s rRNA gene , Alpha & Beta diversity, Relative abundance

Gut-Microbial Diversity in Recurrent Guillain–Barre´ Syndrome

Poster No:
P 389

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Introduction:
Recurrence of Guillain–Barre´ syndrome (RGBS) occurs very rarely with a frequency of 1-3%. Usually, the recurrence occurs after months to years of the initial episode. Gut dysbiosis has been linked to autoimmune responses like GBS. Therefore, the current study was intended to explore the gut-microbial diversity in recurrent GBS compared to non-recurrent patients and healthy controls.

Methods:
All the seven enrolled patients with RGBS had two or more episodes that fulfilled the NINDS criteria for GBS. Gut microbiome of 7 RGBS patients were compared with 7 age-sex-treatment matched GBS patients and 7 age-sex-ethnicity matched controls through sequencing (V4 of 16s rRNA gene) and metagenomic analysis using Qiime2-Dada2 pipeline. We used mean-abundance to compare taxonomy between subgroups and LEfSe analysis to determine deferentially abundant taxa.

Results:
Most of the RGBS patients were highly severe with MRC-sum score 0-20 (4/7, 57%) and 21-40 (28%, 2/7), autonomic dysfunction (57%, 4/7) and supported by mechanical ventilation (72%, 5/7). Taxonomic bar-plot showed, class Gammaproteobacteria was found higher in patients with recurrent GBS (>10%) compared to non-recurrent GBS (4.5%) and healthy controls (<1.0%). However, Firmicutes, Bacteriodota, Actinobacteriota, Euryarchaetota are over presented phylums in RGBS. Comparing the feature taxonomy among electrophysiological subgroups revealed, Prevotellaceae family were more abundant in demyelinating subtype than axonal variant of GBS (32% vs. 14%). Order Enterobacterale are found to be higher (8%) in severe RGBS compared to severe non-recurrent GBS (4%). Alpha and beta-diversity indexes showed no significant differences between RGBS microbiome-diversity and non-recurrent GBS considering disease severity, disease outcome, mechanical ventilation and autonomic-dysfunction. Differential relative abundance analysis (LEfSe) showed no specific taxa as differentially abundant in patients with RGBS compared to GBS and controls.

Conclusions:
We found no significant association of gut-microbiota with recurrent GBS. Further in-depth study is required including large number of RGBS to find the role of Gut-microbiota in RGBS.

References:
No

References 1:

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Grant Support: This research is supported by 'Global Health Equity Scholars NIH FIC TW010540", the Fogarty International Center, National Institute of Neurological Disorders and Stroke of the National Institutes of Health, USA.

Keywords: Recurrent Guillain–Barre´ syndrome, Microbiome , Metagenomics , Alpha diversity , beta-diversity

CD56dim NK Cells Expand in the CSF of Inflammatory Neuropathies

Poster No:
P 390

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Introduction:
Polyneuropathies have many potential causes and it is difficult to distinguish between treatable and untreatable forms. Inflammatory neuropathies, such as chronic inflammatory demyelinating polyneuropathy (CIDP), are generally treatable, but are often misdiagnosed. Using single cell transcriptomics, we previously identified an expansion of cytotoxic T cells and an altered local inter-cellular signaling in an established mouse model of human CIDP. In a flow-cytometry analysis of the CSF, we previously found increased cytotoxic cells in the CSF of CIDP and GBS patients.

Methods:
We performed single cell transcriptomics and immune repertoire analysis of paired CSF and blood samples of CIDP (n = 8), GBS (n = 8), paraproteinemic polyneuropathy (PPN) (n = 6) and chronic idiopathic axonal polyneuropathy (CIAP) (n = 6).

Results:
GBS and CIDP patients exhibited a significant expansion of cytotoxic CD56dim NK cells in the CSF compared to CIAP. CIDP, but not GBS patients, also displayed an increase in a subpopulation of central memory CD4+ T cells compared to CIAP. T cell receptor sequencing revealed a clonal expansion in the CSF of GBS and PPN patients. TCR clones partially overlapped between CSF and blood intra- but not inter-individually.

Conclusions:
We present a single cell transcriptional map of the CSF and blood of different forms of polyneuropathy. Our findings indicate that cytotoxic NK cells may play a crucial role in the pathophysiology, but may also serve as diagnostic biomarkers of inflammatory neuropathies.

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Yes

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Grant Support: M.Heming is supported by the Interdisciplinary Center of Clinical for Clinical Research (IZKF) Münster (SEED/016/21).

Keywords: CIDP, GBS, single cell RNA sequencing, CSF

The SARS-CoV-2-Pandemic And Its Impact On Patients With Chronic Inflammatory Neuropathies

Poster No:
P 391

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Introduction:
COVID-19 pandemic is especially compromising for patients with severe conditions like autoimmune diseases and receiving an immunomodulatory treatment. This study aimed to investigate the longitudinal changes in the health care of patients with immunemediated neuropathies during the COVID-19 pandemic. We present data on vaccination prioritization in the early course of the pandemic along with data on the impact of lockdown and contact restrictions on registry research.

Methods:
We performed a cross-sectional survey using questionnaires in a prospective cohort of patients with immunemediated neuropathies at two timepoints of the pandemic: May-July 2021 and May-July 2022. To evaluate changes in register research, we used nerve conduction studies as a marker for on-site follow-up examinations.

Results:
The cohort consisted of 73 patients (55 male), mean age 61 years. In 2021, 19% of patients reported a reduced number of physician-patient-contacts, only 14% reported this in 2022. However, the overall health-care situation worsened from 2021 to 2022. 15% reported reduced overall health-care situation in 2021, and 26% in 2022. Switching of immunomodulatory treatment and stretching of treatment intervals occurred more often in 2022 than in 2021. In 2021, 29% of patients reported absence of physio-/ergotherapy, 34% reported this in 2022. 50% of patients received a vaccination prioritization certificate at the beginning of the pandemic. At the first timepoint 81% of the patients had received a vaccination offer, 38% of them on the basis of the certificate. There has been a significant decrease in nerve conduction studies coinciding with the lockdown in Germany.

Conclusions:
COVID-19 pandemic has a strong impact on patients with immunemediated neuropathies. Despite relaxations of COVID-19 restrictions, the health-care situation of patients worsened from 2021 to 2022, probably due to changes in treatment and reduced physio-/ergotherapy. Also the register-research could not be continued as before the pandemic.

References:
No

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Grant Support:

Keywords: Sars-CoV-2, impact of COVID-19, chronic inflammatory neuropathies

Magnetic Resonance Imaging Pattern of the Brachial Plexus in Autoimmune Nodopathy

Poster No:
P 392

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Introduction:
Autoimmune nodopathy, previously known as anti-nodal/paranodal antibody positive chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), is characterized by antibodies against molecular in the node of Ranvier and paranodal region. The clinical feature and treatment response of the disease is distinct from that of CIDP. The magnetic resonance imaging (MRI) of the brachial plexus has been widely used in the diagnosis and diffentiation of perpheral neuropathy. In this study, we aim to describe and summarize the pattern of brachial plexus MRI of autoimmune nodopathy.

Methods:
The T2 weighted fat suppression or T2-weighted short tau inversion recovery of brachial plexus MRI studies in autoimmune nodopathy patients were reviewed by two radiologists experienced in peripheral nerve imaging. A composite MRI score (maximum 6) was determined through semi-quantitative evaluation of nerve hypertrophy (0-normal, 1-mild, 2-moderate, 3-severe) and T2 hyperintensity (0-normal, 1-mild, 2-moderate, 3-severe) described by Staff et. al..

Results:
The hypertrophy of the pre-ganglionic part of the brachial plexus was identified in autoimmune nodopathy patients, associated with the elevation of proteins in cerebrospinal fluid. In patients with anti-NF155 antibodies, the hypertrophy of the post-ganglionic part of the brachial plexus was identified, but not in anti-NF186 antibody-positive patients. In patients with long disease duration, the symptoms could resolve while the hypertrophy of the brachial plexus still exist after several sessions of treatment. In addition, the brachial plexus was uneven in MRI, indicating chronic pathological changes of the nerve.

Conclusions:
In the MRI studies of the brachial plexus in autoimmune nodopathy, we identified a distinct pattern, and the pattern may vary in patients with different antibodies. These findings may reflect the nature of the disease, and indicate the prognosis of autoimmune nodopathy patients.

References:
No

References 1:

References 2:

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Grant Support:

Keywords: Autoimmune Nodopathy, Chronic Inflammatory Demyelinating Polyradiculoneuropathy, Magnetic Resonance Imaging

Guillain–Barré syndrome in low-resourced countries- the need for simple clinical algorithms

Poster No:
P 393

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Introduction:
Electrophysiologic evaluation is important in the diagnosis of Guillain–Barré syndrome (GBS). In under-resourced regions of the world, reliable and cost-effective electrodiagnostic tests are largely unavailable; making simple clinical algorithms the cornerstone of timely GBS diagnosis

Methods:
An illustrative case-report.

Results:
A 59-year-old female developed progressive weakness and numbness of both lower and then upper limbs. The local health care personnel did not recognize the signs of GBS and diagnosis was delayed. She then developed bulbar and respiratory weakness and was emergently admitted for invasive ventilatory support. Examination revealed signs consistent with; 1) lower motor neuron pathology, in particular, areflexia, 2) severe proximal more than distal weakness, and 3) distal predominant sensory loss. These finding were consistent with either an acute polyneuroradiculopathy like GBS or acute cervical myelopathy. 4) However, the presence of bulbar weakness and other cranial nerve deficits favoured GBS. With this simple 4-step clinical algorithm the diagnosis of GBS was confirmed and patient was started on intravenous immunoglobulin on day 6 of illness. Electrodiagnosis is not available in Laos. By day 8, patient started to improve and was discharged on day 14. At 1.5 months, she had fully recovered.

Conclusions:
In parts of the word where electrodiagnosis and spinal fluid analysis are costly and not available or reliable, it is important to adopt a simple clinical algorithm that would raise the suspicion of GBS early. This allows the patients to be sent to a facility that can manage the monitoring and supportive care required of GBS. Likewise, an easy-to-follow clinical algorithm for the comprehensive management of GBS is, 'Diagnosis and management of Guillain–Barré syndrome in ten steps' by Leonard et al.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: no

Keywords: a simple clinical algorithm raises the suspicion of GBS early.

Liver Function Abnormalities Are a Feature of Guillain-Barré Syndrome

Poster No:
P 394

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Introduction:
Guillain-Barré syndrome (GBS) is an antibody-mediated autoimmune disease characterized by peripheral nerve damage mediated by classical complement pathway activation. This study evaluates liver function abnormalities (LFTs) often seen in patients with GBS.

Methods:
GBS-01 (N=50) was a randomized placebo-controlled study of escalating doses of ANX005 in patients recently diagnosed with severe GBS. Patients received a single dose of ANX005 (n=38) or best supportive care (n=12). Serum samples collected at baseline and weeks 2, 4 and 8 were assessed at a central laboratory.

Results:
In GBS-01, 36 patients (95%) receiving ANX005 and 11 patients (92%) receiving best supportive care had an ALT elevation (>ULN) during their disease. Elevated serum ALT was associated with an AST/ALT ratio <1.0, suggesting a hepatic origin and accompanied by lesser increases in gamma-glutamyl transferase (γGT) and aspartate aminotransferase (AST) but not bilirubin. ALT levels followed the course of GBS, peaking at day 8. At baseline, 48% of patients had elevated ALT (mean, 38.44 IU/L; SD, ±28.53), rising to 76% of patients at day 8 (mean, 124.51 IU/L; SD, ±278.07) and returning towards baseline at day 56 (mean, 58.63 IU/L; SD, ±31.67). At peak, 14% of patients had ALT levels >4×ULN, 20% had ALT levels >2.5 to ≤4.0×ULN, and 32% had ALT levels >1.5 to ≤2.5×ULN. There was no difference in peak ALT levels between placebo (median ALT 2.8×ULN) and ANX005 (median ALT 2.5×ULN) (t-test, p=0.63). There was no association with preceding diarrhea (p=0.26) or disease severity such as MRC sum score at nadir or serum peak NfL.

Conclusions:
Transient elevated ALT follows the monophasic course of GBS and is associated with increases in γGT and AST. Extensive peripheral nerve damage with release of nerve lipids may be responsible for elevated LFTs. Metabolomic and lipidomic research is in progress to understand these findings.

References:
No

References 1:

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References 3:

References 4:

Grant Support: Supported by Annexon Biosciences

Keywords: Guillain-Barré syndrome, complement, ANX005, outcomes

Hypoalbuminemia association with severe Guillain-Barré syndrome: an update of a prospective cohort study

Poster No:
P 395

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Introduction:
Guillain-Barre syndrome (GBS), an immune-mediated polyneuropathy with variable clinical manifestation, prognosis and outcome. Despite of the proven efficacy of intravenous immunoglobulin (IVIg), 20% patients remain disabled with 2-19% mortality. Identification of biomarkers associated with disease prognosis and the clinical outcome is crucial to improve clinical management and effective treatment. Therefore, we investigated biomarkers to predict the severe GBS and clinical outcome.

Methods:
We included 172 GBS patients in a prospective cohort study during 2019-2022 in Bangladesh. Detailed neurological examinations, serological investigations including serum albumin and serum IgG were performed at baseline and pre-defined follow-up. Statistical comparisons between intended biomarkers and disease prognosis were performed using spearman correlation, ANOVA and student t-test.

Results:
The median age of patients was 31 years (IQR: 22-40) with male predominance (70%); 60% patients were treated with either IVIg or plasmapheresis and remaining patients received only supportive care. Severe GBS (GBS-DS>3) was found among 88% patients and 32% patients required mechanical ventilation. Serum albumin levels showed strong negative correlation with GBS disability score at enrolment ($p<0.001$) and 2 weeks ($p<0.001$). Severely affected patients with GBS had significantly lower serum albumin level than mild GBS (38.8g/L vs. 42.9 g/L, P=<0.001) at enrolment. At 2 weeks, serum albumin level declined significantly (P=0.002), whereas serum IgG increase ($p<0.001$) among the treated patients compared to supportive care patients. Significant increase of serum albumin was noted after 13 weeks among treated patients compared to supportive care patients ($p<0.0001$). At 26 weeks, the median serum albumin levels were decreased in poor outcome patients compared to patients with good outcome, but no significant association was found.

Conclusions:
Decreased serum albumin and elevated serum IgG levels can be considered as potential marker for disease severity and predictors of treatment response of GBS. Detail investigation is warranted to validate the clinical relevance of these biomarkers in future.

References:
No

References 1:

References 2:

References 3:

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Grant Support:

Keywords: Guillain-Barré syndrome, Biomarker, Hypoalbuminemia

Gut microbiota diversity in the pathogenesis of Guillain–Barré syndrome: a prospective study

Poster No:
P 396

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Introduction:
The predisposing factors that develop Guillain–Barré syndrome (GBS) after infection are unknown. We hypothesized that one of these factors is the gastro-intestinal microbiota. Therefore, we investigated gut-microbiota diversity in GBS patients and healthy controls (HCs) to identify potential biomarker associated with GBS in order to generate plausible hypothesis that can be tested in follow-up studies.

Methods:
We compare phylotype profiles of gut-microbiota of GBS patients (N=57) at enrolment and after 6-months follow-up (N=32), with age-and gender-matched HCs (N=57) using V4-region sequencing of 16S ribosomal RNA. Severe GBS was categorized with GBS-disability score ≥ 3. Sequence data was analyzed using Qiime2-Dada2 pipeline. Alpha and beta diversity metrics were compared with pairwise permanova and kruskal-wallis tests. Logarithmic Discriminant Analysis (LDA) score was used to identify biomarker potential.

Results:
Patient's median (IQR) age was 33 (40–25) years; 65% were male and 83% were severely affected indicated by their inability to walk independently. GBS patients revealed high abundance of Parabacteroides, Bacteroides, UCG_003, and Bilophila, whereas HCs were highly abundant with Alloprevotella, Ruminococcus and Oribacterium. Microbial community evenness and richness of GBS were significantly different than HCs and showed significant (p=0.001) distinct phylogeny and relative abundances (RA). Taxonomic classification revealed, Firmicutes and Bacteroidota were the most abundant phylums in both GBS and HCs. Severe GBS showed significant gut-microbial beta-diversity (p=0.011) compared to mild GBS. After 26 weeks, microbial community evenness and richness, phylogeny, and RA were significantly different than acute GBS and HCs. Two genus, Bacteroides and Parabacteroides showed significant potential as biomarker with high differential RA (LDA >3.0) in GBS than HCs.

Conclusions:
Our data indicated that gut-microbiota are associated with development of GBS, its severity and outcome. Taxa with differential RA have biomarker potential for GBS. Systematic meta-genomics studies are warranted to further characterize these potential biomarkers for GBS and develop future hypothesis-driven clinical studies.

References:
No

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References 2:

References 3:

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Grant Support: Swedish International Development Cooperation Agency

Keywords: Guillain–Barré syndrome, Gut microbiota , Pathogenesis, Biomarker

Myelitis And Ganglionitis In Leprosy: Extensive Imaging Impairment With No Clinical Correlation

Poster No:
P 397

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Introduction:
Leprosy usually manifests itself in the skin and peripheral nerves, reports of involvement of the central nervous system (CNS) are scarce in the literature.

Methods:
A 35 yr old male refers paresthesia on the medial surface of the right(R) forearm and hand for five months. He developed hypoesthesia and paresis of the 4th/5th fingers as painful to the touch nodulation above medial epicondyle. Dermatological evaluation and Bacilloscopy were negative. Neurological examination: thickening of the R Ulnar nerve (UN) above the elbow. Hypoesthesia tactile, thermal and painful anesthesia in the RUN and hypoesthesia in all modalities in the R medial cutaneous (MCF) nerve. Paresis in the right hypothenar musculature.

Results:
Liquor analysis was nonspecific lympho/mononuclear pleocytosis and proteinorrachia. Neurophysiological tests: absence of sensory response in the RU and RMCF nerves and motor response in the RUN. Ultrasound (US) increase in the cross-sectional area from the forearm to the axilla, morphological abnormalities and flow on Power Doppler in these nerves. Cervical spine/brachial plexus Magnetic Resonance reveals elongated right intramedullary expansive lesion T2 and STIR hypersignal C6-D1, with intense contrast enhancement extending to the dorsal root ganglion. Neurography of RUN: expressive thickening heterogeneous fascicular from the roots of C8-T1 to the elbow, RMCFN equally thickened, and both with hyperintense T1 and multiple minilobulations inside with contrast enhancement. PET/CT uptake of 18F fluordeoxyglucose on respective nerves. USG-guided biopsy RMCFN evidenced inflammatory chronic neuropathy with granulomas and BAAR. The diagnosis of pure neural form of leprosy was made and polychemotherapy started as well as corticosteroids pulse therapy due to the intense neurological involvement.

Conclusions:
Physiopathological damage in leprosy is not well defined. This report demonstrates the dissociation between the extent of neurological impairment identified by image and the clinical/neurophysiological deficit. The CNS involvement in leprosy may be more extensive than described in literature, even in paucibacillary patients.

References:

No

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References 3:

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Grant Support:

Keywords: leprae, myelitis, atypical, Image

Possible Applicability of 18F-FDG PET/CT in the Evaluation of Lepromatous Leprosy Peripheral Neuropathy: Case Series

Poster No:
P 398

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Introduction:
Leprosy is caused by multiple interactions between Mycobacterium leprae (M. leprae) and the host's peripheral nerve cells. The pathophysiological mechanisms of nerve damage in the lepromatous pole of leprosy remain poorly understood. The findings of 18F-FDG PET/CT on the peripheral nerves of three lepromatous patients were used to evaluate the degree of peripheral nerve uptake of glucose, comparing them with clinical, electrophysiological, and histopathological evaluations.

Methods:
We report three cases of peripheral neuropathy in lepromatous leprosy. Patients were evaluated up to 3 months after leprosy diagnosis using neurological examination, nerve conduction study and 18F-FDG PET/CT; none of them had other comorbidities associated with peripheral neuropathy.

Results:
In the first case, we describe a 23-year-old-male with clinical symptoms e signs of acute neuritis of the left ulnar nerve, six months after starting multidrug treatment (MDT) for lepromatous leprosy; there was uptake of 18F-FDG in the ulnar nerve bilaterally. The second case, a 47 year-old male, was evaluated at the beginning of MDT and had no signs or symptoms of peripheral nerve damage on neurological examination, however, nerve conduction studies (NCS) showed diffuse alterations, with a pattern of multiple mononeuropathies; there was no 18F-FDG uptake in any peripheral nerve. The last case is a 70-year-old man, with complaints of paresthesia in the legs and hands that started 1 year before the diagnosis of lepromatous leprosy. Neurological examination and nerve conduction studies showed alterations compatible with axonal predominant sensorimotor polyneuropathy. There was no 18F-FDG uptake in any peripheral nerve.

Conclusions:
18F-FDG PET-CT can be a useful tool to confirm neuritis, especially in cases that are difficult to diagnose, such as pure neural forms, and for the differential diagnosis between a new episode of neuritis and chronic neuropathy.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: 18F-FDG PET/CT imaging, Peripheral Neuropathy, Lepromatous leprosy, Pathophysiological mechanisms

Is everything leprosy? Experience with nerve biopsy in a reference center for the condition

Poster No:
P 399

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Introduction:
Brazil is the 2nd country with the highest number of leprosy cases in the world, with approximately 18,000 cases reported in 2020 alone. There are some centers specializing in the diagnosis, treatment, and monitoring of the disease. This study aimed to describe the nerve biopsy experience of an outpatient clinic specializing in leprosy.

Methods:
We performed a retrospective analysis of the nerve biopsies database in the last 24 years, with cases ranging from 1998 to 2022. Each material was fixed in glutaraldehyde, 10% formalin, and frozen in liquid nitrogen. For those embedded in paraffin, the sections were stained with hematoxylin and eosin, Fite-Faraco, and Gomori's trichrome; and semi-thin sections were stained with Toluidine Blue. The laboratory used frozen material for molecular testing and research projects.

Results:
We found 807 nerve biopsy records and of these, 29 biopsies did not contain peripheral nerve material (3.6%). Of the remaining 778 cases, 319 (41%) were diagnosed as leprosy. For more than 60 patients with a suspected pure neural form of leprosy (without dermatological lesion), the disease was confirmed. Other diagnoses were: vasculitis (4.6%), diabetic neuropathy (3.5%), compression neuropathy (2.4%), amyloidosis (1.2%), CIDP (0.6%), alcoholic neuropathy (0.4%), MADSAM (0.3%), among others. About 337 cases (43.3%) had no definitive diagnosis, only histopathological description; some of these cases (55) were of 'neuritis', without a conclusion. The diagnosis rate using nerve biopsy, other complementary tests, and clinical sessions was 56.7%. The most biopsied nerves were the sural nerve, the cutaneous branch of ulnar nerve, and the superficial peroneal nerve.

Conclusions:
Nerve biopsy was useful for detecting leprosy, especially in the pure neural form. Although the country has a high prevalence and incidence of leprosy, attention should be paid to other hypotheses. The clinical-pathological correlation was essential for the final diagnosis of the patients.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Sural nerve, Biopsy, Leprosy, Database

COVID-19 Associated Guillain-Barré Syndrome: Report of 5 Cases

Poster No:
P 400

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Introduction:
Guillain-Barré syndrome (GBS) is a post infectious inflammatory polyradiculoneuropathy associated with numerous infections. There are also many GBS cases reported to be associated with coronavirus disease-2019 (COVID-19). In this report we aimed to present 5 cases of GBS that were followed by confirmed COVID-19 infection.

Methods:
The average age was 63.2 (48-81) years, four of them were male (80%). All cases were SARS-CoV-2 PCR positive, and the average time interval from infection to GBS symptoms was 20.2 days.

Results:
The clinical presentation patterns were similar to non COVID-19 associated GBS patients. Nerve conduction studies were considered demyelinating in four, axonal in one of cases. Three of cases were classic sensorimotor GBS variant. Cerebrospinal fluid assessment demonstrated albuminocytologic dissociation in all of 5 cases. All cases showed a good prognosis after treatment with intravenous immunoglobulin and none of them required intensive care. After discharge, the average follow-up period was 21.2 months, and chronic inflammatory demyelinating polyneuropathy did not develop in any patient.

Conclusions:
The time interval between COVID-19 infection and the occurring GBS symptoms suggests a COVID-19 associated postinfectious mechanism in these patients. Most studies reported classic sensorimotor demyelinating GBS, and COVID-19 associated and classic non-COVID-19 associated GBS should be thought to have possibly the same pathogenetic mechanisms. To clarify this issue, future studies and comparisons are needed.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: COVID-19, Guillain-Barré syndrome , SARS-CoV-2

Thymoma-associated pure red cell aplasia initially presenting as chronic immune-mediated neuropathies

Poster No:
P 401

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Introduction:
Pure red cell aplasia (PRCA) is a rare disorder characterized by severe anemia due to erythropoiesis failure in the bone marrow. Secondary PRCA may be associated with underlying diseases such as tumors, hematologic malignancies, autoimmune diseases, or infections. Thymoma-associated PRCA comprises a considerable proportion of secondary PRCA, and is thought to be an organ-specific autoimmune disease. We describe a patient with thymoma-associated PRCA initially presenting as chronic inflammatory axonal neuropathy (CIAN).

Methods:
A 70-year-old woman presented with a several-months history of progressive motor weakness in four limbs. She has never complained of sensory disturbance and became unable to walk independently over time. Neurologic examination showed bilaterally-symmetric distal-dominant weakness without sensory loss, generalized areflexia, and mild atrophy in intrinsic hand muscles on both sides. Extensive evaluation was performed, including nerve conduction study (NCS), electromyography (EMG), serologic tests, and lumbar puncture.

Results:
NCS showed prolonged distal latencies, significantly reduced compound motor action potentials amplitudes, and relatively spared nerve conduction velocities. EMG showed abnormal spontaneous activities with chronic neurogenic change. The repetitive nerve stimulation test was unremarkable. Cerebrospinal fluid examination revealed albuminocytologic dissociation. The serologic test showed positivity for acetylcholine receptor antibody (0.87 nmol/L) and anti-ganglioside GM1 antibody. The patient was suspected of having CIAN. Meanwhile, the blood test showed profound normocytic anemia (hemoglobin: 6.4g/dl) with low reticulocyte count and elevated serum ferritin level (785ng/ml). The result of the bone marrow biopsy suggested PRCA. Chest computed tomography showed a 4.1 x 3.7 cm well-defined heterogeneously enhancing mass in the mediastinum, which turned out to be spindle cell type thymoma after surgical resection. Ultimately, the patient was diagnosed with CIAN complicated with thymoma-associated PRCA. The patient was dramatically improved after intravenous methylprednisolone and additional intravenous immunoglobulin G (IVIg) infusion.

Conclusions:
Thymoma-associated PRCA can be accompanied by chronic immune-meidated polyneuropathies, which showed an excellent response to the immunotherapies, including corticosteroids and IVIg.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: chronic inflammatory polyradiculopathy, autoimmune diseases, thymoma, pure red cell aplasia

Magnetic Resonance Neurography Findings in Patients with Chronic Inflammatory Demyelinating Polyneuropathy

Poster No:
P 402

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Introduction:
Diagnosis of chronic inflammatory demyelinating polyneuropathy (CIDP) lacks a single gold standard test and depends on a combination of clinical, electrodiagnostic, and laboratory findings. Whole body magnetic resonance neurography (MRN) is an imaging technique can show diffuse inflammatory nerve changes which can be used to support the diagnosis of CIDP. In the present study we aimed to investigate the diagnostic value of whole body MRN and its potential as a disease monitoring tool after immunotherapy in a group of treatment-naïve CIDP patients.

Methods:
Whole body MRN was performed in 10 CIDP patients and 7 healthy controls at baseline and 3-4 months after immunotherapy in the CIDP group. Baseline clinical neuropathy scales, electrophysiologic parameters, and MRN imaging findings were compared before and after treatment in CIDP patients.

Results:
We found highly concordant symmetrical thickening and increased T2 signal intensities in the brachial/lumbosacral plexus, femoral, or sciatic nerves in 70% of the patients and none of the healthy controls. We did not find any significant difference in clinical or electrophysiologic outcomes measures pre- and post-treatment. There was incidental findings including signal changes in the muscles, bony lesions, organomegaly and lymphadenopathy in two of patients who were ultimately diagnosed with POEMS (polyneuropathy, organomegaly, endocrinopathy, M-protein, skin changes) syndrome.

Conclusions:
MRN imaging has a good sensitivity in detecting abnormalities in proximal nerve segments in patients with CIDP, and can be helpful in identifying alternate diagnoses such as POEMS syndrome . As no treatment related imaging changes were seen, future studies evaluating the role of MRN in assessing treatment responsive should consider a time interval between scans of longer than 4 months.

References:
No

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References 3:

References 4:

Grant Support: The authors would like to thank and acknowledge the CIDP Foundation International for funding this work through a research grant.

Keywords: CIDP, Neurography, Immune neuropathy, MRI

The proteome of POEMS syndrome

Poster No:
P 403

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Introduction:
The pathogenesis of POEMS syndrome is not yet understood. The presence of a monoclonal lambda restricted plasma cell dyscrasia is associated with cytokine release and mechanisms leading to down-stream multi-organ dysfunction, including a disabling inflammatory neuropathy. This study aimed to explore the proteome of POEMS syndrome through unselective and an inflammatory targeted mass spectrometry approach to identify major proteome disturbances and biomarkers that might enlighten mechanistic pathways involved in disease.

Methods:
Participants were recruited to the study from our UK POEMS Database fulfilling the diagnostic criteria for POEMS syndrome. Pre-treatment, post-treatment and relapse sera were selected. Sera from POEMS syndrome patients were compared to that of CIDP, multiple myeloma and healthy controls. An untargeted 'shotgun' proteomic analysis was performed on pre-treatment sera only, followed by a targeted analysis using a pre-defined inflammatory panel of 80 peptides.

Results:
Differences and commonalities in proteome perturbations between POEMS and CIDP were identified. Ingenuity Pathway Analysis and STRING (Search Tool for the Retrieval of Interacting Genes) demonstrated humoral response proteins, inflammation, haematological disease, cardiovascular disease and organismal injury (involving blood clots, thrombi, vaso-occlusion and stroke) pathways as being most likely activated. ICAM-1 and neurofilament medium chain were proteins identified on targeted study which may be specifically related to POEMS neuropathy.

Conclusions:
POEMS syndrome is a rare multi-system condition in which immune system activation results in several downstream processes involving the humoral system, inflammation, hypercoagulation and organismal injury. These data provide insights into disease pathways that might be involved in pathogenesis and exploited in treatment.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: Dr Keddie was funded by the Association of British Neurologists and Guarantors of Brain

Keywords: POEMS, Mass spectrometry , Biomarkers, Neuropathy

An Exploratory Study of Neuromuscular Magnetic Resonance Imaging in POEMS syndrome

Poster No:
P 404

Authors:
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Institutions:
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Introduction:
Magnetic resonance imaging (MRI) of lower limb intramuscular water and fat distribution correlates with functional measures in inherited Charcot-Marie-Tooth (CMT)1A neuropathy, with superior responsiveness to existing measures. MRI quantification of lumbosacral nerve root and sciatic nerve hypertrophy is also a biomarker included in supportive criteria for chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal protein and Skin changes syndrome (POEMS) is a treatable multisystem disorder with a characteristic, often severe conduction-slowing neuropathy. Like CMT1A the neuropathy is length-dependent and results in muscle atrophy and presumably fatty replacement. There are no existing biomarkers that reliably predict long-term outcome in POEMS. We performed a pilot study of neuromuscular MRI in POEMS, to explore has any potential for MRI in quantifying disease activity and estimating long-term outcome.

Methods:
10 patients with POEMS at various stages of treatment were recruited for neuromuscular MRI of the lower limbs . Clinical scores including i-RODS and MRC scores were collected to assess disability and impairment. Thigh and calf muscles were imaged for water-T2 measurement 3-point Dixon fat quantification and diffusion weighting, to measure acute denervation and chronic fatty atrophy relating to axonal damage. The lumbosacral plexus was also imaged with high resolution structural and STIR (short tau inversion recovery) imaging and the sciatic nerve with axial 3-dimensional STIR and diffusion weighted imaging, examining for hypertrophy and signal change.

Results:
We will present the results of this pilot study of neuromuscular MRI of patients with POEMS to determine whether particular sequences appear to reflect POEMS disease activity and treatment outcomes. Analysis is ongoing.

Conclusions:
-

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: Study is supported by a research grant from GBS CIDP FI.

Keywords: POEMS syndrome, Neuromuscular magnetic resonance imaging

Improving protocol of giving IVIG in early Plateau phase in Guillain Barre syndrome for reducing mortality and disability rate

Poster No:
P 405

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Introduction:
Guillain–Barré syndrome (GBS) is an acute, immune-mediated polyneuropathy that often leads to severe weakness. About 25% of patients need artificial ventilation and 20% are still unable to walk unaided after 6 months. Intravenous immunoglobulin (IVIG) is a proven effective treatment for GBS. GBS patients being unable to walk unaided are currently treated with a standard single IVIg dose (0.4 g/kg bodyweight for 5 days). The estimated annual cost of GBS was $1.7 billion, including $0.2 billion in direct medical costs and $1.5 billion in indirect costs. Most of the medical costs were for community hospital admissions. Most of the indirect costs were due to premature deaths. The mean cost per patient with GBS was $318,966. The economic cost of Guillain-Barré syndrome was substantial, and largely due to disability and death. The cost estimate summarizes the lifetime health burden due to GBS in monetary terms, and provides some of the information needed to assess the costeffectiveness of health measures that affect GBS. In Asia there are 5469 patients with GBS between 2000-2013, As the inpatient mortality rate was 1.61% and 55 deaths occurred before day 19 Otherwise, In Korea they reported that among 10,114 patients of GBS being diagnosed during 2002-2018, there were 502 patients had moderate disability and 526 had severe disability by the end of the study period and unfortunately there were 144 patients' in-hospital deaths.

Methods:
All patients who is diagnosed Guillain Barre syndrome with progressive phase

Results:
Expectation: To identify the subtype of Guillain Barre syndrome To evaluate the mortality and disability post infection To compare data based past and present

Conclusions:
Concern about the Mortality and disability in GBS patients especially comorbidity for management efficiency and saving patient's life

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Mortality , Disability , Before Plateau phase, IVIG

COVID-19 vaccination and azathioprine can be worsening factors for focal chronic inflammatory demyelinating polyneuropathy

Poster No:
P 406

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Introduction:
Several factors as steroid or cold are known as risk factors for clinical worsening in motor dominant chronic inflammatory demyelinating polyneuropathy (CIDP) or multifocal motor neuropathy.

Methods:
Here we report a case focal CIDP presenting as brachial plexopathy which experienced deterioration after Jassen COVID-19 vaccine and also after using azathioprine.

Results:
A 33-year old-man came for left distal hand weakness and numbness since 6 months. Left finger flexion and extension, abduction showed motor weakness (medical research council grade 3), left elbow flexion weakness (medical research council grade 4-) with distal hand atrophy. Tendon reflexes were reduced in four limbs. Nerve conduction study and electromyography results were consistent with left pan-brachial plexopathy. Cerebrospinal fluid study showed albumincytologic dissociation with mild protein elevation. Brachial plexus MRI showed thickening and increased T2 signal of the left brachial plexus. Cervical spine MRI was normal. When intravenous high dose methylprednisolone infused, patient developed hoarseness with significantly aggravated left arm weakness. After cessation of steroid and start of intravenous immunoglobulin G, his weakness was nearly full recovered. He monthly received intravenous immunoglobulin G to maintain these improvements. In 2020, patient had Jassen COVID-19 vaccination and this events significantly aggravated his arm weakness even with intravenous immunoglobulin G maintenance. In 2022, due to economical cause, patient wanted to try other immunosuppressant medications for CIDP and azathioprine was started without steroid medication. After 3 weeks, he experience rapid aggravation of left arm weakness with hoarseness and stopped azathioprine which reverse the weakness.

Conclusions:
Treatment response and risk factor for deterioration may differ in CIDP variants compare to typical CIDP. Careful monitoring is necessary for deterioration when using immunologically acting drug especially in CIDP variants.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: chronic inflammatory demyelinating polyneuropathy, COVID-19 vaccination, azathiorpine, CIDP variants

Accuracy of polyclonal secondary antibodies specific for gamma-chain of MOG-IgG: Comparison with the anti-IgG1Fc secondary antibodies

Poster No:
P 407

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Introduction:
Myelin oligodendrocyte glycoprotein immunoglobulin G (IgG) associated disorder (MOGAD) is an inflammatory demyelinating disease (IDD) of the central nervous system (CNS) that features anti-MOG antibody (MOG-IgG). Serostatus of MOG-IgG is crucial to diagnose MOGAD and anti-IgG Fc and anti-IgG1 Abs are highly recommended secondary Abs in the detection of MOG-IgG. To explore the accuracy of polyclonal secondary Ab specific for IgG gamma chain, which detect all subclasses of IgG, we compared it to previously established anti-IgG1Fc secondary Ab.

Methods:
Serum samples from 217 patients were tested using anti-IgG1 Fc Abs and anti-IgG gamma chain Abs. Cutoff value for serum positivity for MOG-IgG was determined by six standard deviations above the average of mean fluorescence ratio of negative controls. Sensitivity was calculated as the percentage of positive cases within the patients who were consistent with MOGAD phenotypes. Specificity was calculated as the percentage of negative cases within the patients who were inconsistent with MOGAD phenotype.

Results:
164/217 patients were classified as suspected IDD of the CNS. The cutoff values were 2.66 for anti-IgG1 Fc Ab and 2.89 for anti-IgG gamma chain Ab. Of the 217 patients' samples, 214 samples were concordant in both assays. Anti-IgG gamma chain Abs detected one more patient in ADEM group. In ON, two cases showed discrepancies in anti-IgG1Fc and anti-IgG gamma chain Abs. Sensitivity was slightly higher when anti-IgG gamma chain Abs were used. Specificity were 100% for both secondary Abs.

Conclusions:
Anti-IgG gamma chain Ab revealed a higher sensitivity and a same specificity for the detection of MOG-IgG than anti-IgG1Fc Ab. As anti-IgG gamma chain Ab is polyclonal Ab which can detect all subclasses of IgG, it might detect an IgG subclass other than IgG1. We suggest that anti-IgG gamma chain Ab, a polyclonal Ab might be used as a complementary method for previously established anti-IgG1Fc Ab.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: MOGAD, MOG-IgG, IgG1

In Vivo Visualization of Eosinophil Degranulation in Eosinophilic Granulomatosis with Polyangiitis: an Ultrastructural Study

Poster No:
P 408

Authors:
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Introduction:
Although eosinophilic granulomatosis with polyangiitis (EGPA) has been considered as a disease belonging to anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis, several studies have suggested that the mechanisms associated with eosinophils play a vital role in tissue damage.

Methods:
We investigated the electron microscopic findings of sural nerve biopsy specimens obtained from 18 patients with EGPA by focusing on the morphology of eosinophils, particularly the mode of degranulation.

Results:
Among a total of 1777 eosinophils evaluated to determine the frequency of degranulation, 1442 (81%) showed findings suggestive of piecemeal degranulation defined as the presence of characteristic eosinophil sombrero vesicles accompanied by alteration of nearby specific granules. The percentages of eosinophils with these findings in the extravascular interstitium and vascular lumen were 80% (937 of 1171) and 83% (505 of 606), respectively. Eosinophils directly releasing their specific granules into the extracellular space by cytolysis were occasionally observed. The percentages of cytolytic eosinophils in the extracellular interstitium and vascular lumen were 6% (66 of 1171) and 1% (7 of 606), respectively ($p < 0.0001$). In the vascular lumen, eosinophils completely devoid of the plasma membrane, appearing to be just releasing their intracellular components into the bloodstream, were observed. Fibrin strands were abundant in these eosinophils. In addition, several platelets were located among fibrin strands, suggesting that coagulopathy occurs in EGPA. With respect to the ANCA status, findings suggestive of cytolysis were observed in 2% (7 of 356) of eosinophils from patients positive for ANCA and 5% (66 of 1421) of eosinophils from those negative for ANCA ($p < 0.05$).

Conclusions:
Both extravascular and intravascular eosinophils can induce tissue damage unrelated to classical necrotizing vasculitis associated with ANCA in patients with EGPA.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: eosinophil

Abundant Fasciculations Are Associated With Increased Persistent Na+ Currents In Chronic Inflammatory Demyelinating Polyneuropathy

Poster No:
P 409

Authors:
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Institutions:
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Introduction:
Patients with established chronic inflammatory demyelinating polyneuropathy (CIDP) present variable degrees of fasciculations. A plethora of changes in electrical properties of the motor axons were reported in CIDP. The aim of this study was to assess which, if any, of such excitability abnormalities of the distal motor axons are particularly associated with fasciculations.

Methods:
Investigations were carried out in 19 patients with established CIDP (age 23-78 years) and 79 healthy controls (age 22-73 years). Multiple measures of motor axon excitability by threshold-tracking were obtained by stimulating the median nerve at wrist and recording the compound muscle action potentials from the abductor pollicis brevis (APB) muscle. EMG recordings were carried out from APB in all the patients.

Results:
A group of 9 of 19 CIDP patients presented abundant fasciculations, identified in more than 4 of 10 examined sites at EMG. These patients had a strength-duration time constant (SDTC) of 0.497 ms which was larger than 0.413 ms ($p<0.05$) in the other patients. As compared to the healthy controls, only the patients with abundant fasciculations showed an increased SDTC, associated with increased threshold deviations during depolarizing electrotonus and a reduced refractoriness at 2 ms after the stimulus during the recovery cycle from 25% to 15%. Simulations using the Bostock's myelinated axon model optimized on healthy controls indicated that these concordant abnormalities could be reproduced by increasing the fraction of the persistent Na+ current from 1.07 to 1.29%.

Conclusions:
Our data suggest that CIDP patients with abundant fasciculations may have a distinct axonal excitability profile with increased SDTC and other excitability changes that are consistent with increased persistent Na+ currents. Given that the increased Na+ load is neurotoxic, these electrophysiological features could indicate neuropathy severity.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: Takeda Pharma

Keywords: CIDP, Fasciculations, Excitability, Axon, Sodium current

Enhancement effect of phosphatidic acid on IgM reactivities to GM1 in multifocal motor neuropathy

Poster No:
P 410

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Institutions:
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Introduction:
Phosphatidic acid (PA), which is one of the acidic phospholipids, increases the reactivities of IgG anti-GM1 antibody in Guillain-Barré syndrome (GBS). Herein, we investigated the effects of PA on IgM anti-GM1 antibody in multifocal motor neuropathy (MMN).

Methods:
We examined IgM antibodies to isolated GM1 and GM1-added with PA (GM1/PA) in 37 MMN patients and 48 control subjects including 24 with amyotrophic lateral sclerosis (ALS) and 24 healthy subjects (HC) using ELISA. We defined that IgM reactivities specific to GM1/PA were positive when the reactivities were as follows; 1) Optical densities (ODs) of IgM reactivities to GM1/PA were higher than 0.1 in subjects without IgM reactivities to both GM1 and PA and 2) ODs of IgM reactivities to GM1/PA were 0.2 higher than ODs of IgM antibodies to GM1 in subjects with IgM anti-GM1 antibodies.

Results:
IgM anti-GM1 antibodies were positive in 20 (54%) with MMN and two (4%) controls (one in HC and one in ALS). The IgM reactivities specific to GM1/PA were detected in nine (24%) with MMN and three (6%) controls (all in HC) ($p<0.05$). Antibody reactivities against GM1/PA were higher than those against GM1 in MMN ($p<0.0001$). Additionally, the change of antibody titers was greater in MMN compared to controls ($p<0.01$). Overall, the numbers of patients who had either IgM anti-GM1 antibody or IgM antibody specific to GM1/PA were 26 (70%) in MMN and four (8%) in controls, respectively ($p<0.01$). Its sensitivity and specificity were 70% and 91%.

Conclusions:
PA enhances IgM reactivities to GM1 in MMN. IgM antibodies to GM1/PA may be useful as a diagnostic marker for MMN.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: GM1 antibody, Phosphatidic acid, Multifocal motor neuropathy

Anti MAG antibody that simultaneously invades the central nervous system and the peripheral nervous system

Poster No:
P 411

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Introduction:
Myelin-associated glycoprotein (MAG) is a transmembrane protein and constituent of myelin in the central nervous system (CNS) and peripheral nervous system (PNS). Anti-MAG antibody (MAGAb) has been a well-noticed association with demyelinating peripheral polyneuropathy, but CNS invasion by the MAGAb is little known. We report a patient with the simultaneous invasion of the CNS and PNS of MAGAb.

Methods:
This is a case report.

Results:
A previously healthy 56-year-old man visited our hospital complaining of right leg weakness (the Medical Research Council [MRC] grade IV) and paresthesia below both knees accompanied by acute urinary retention one day ago. The diffusion-restricted lesion was observed in the left parietal lobe with brain magnetic resonance images (MRI). This lesion showed T2-high signal intensity without contrast enhancement in the consistent area on T1-weighted imaging. Electrodiagnostic studies revealed axonal-type sensorimotor polyneuropathy. Left leg weakness occurred with MRC grade II three days after admission. Spine MRI showed a T2-high signal intensity lesion in the left posterolateral aspect of the T4 spinal cord. Extensive examinations, including serologic, immunologic, neoplastic, and paraneoplastic tests, were performed, and IgM-lambda type monoclonal protein was detected with serum and cerebrospinal fluid immunofixation electrophoresis. MAGAb was detected in his serum, but anti-ganglioside antibodies were not. His symptoms did not improve, and electrophysiologic parameters were deteriorating, despite treatment with intravenous steroids and immunoglobulin. Plasma exchange and subsequent intravenous rituximab infusion were carried out. His urinary retention was maintained; however, lower limb weakness was significantly improved.

Conclusions:
Previous studies of MAGAb-positive patients with CNS invasion were clinically suspected by delayed latencies of somatosensory evoked potentials in the spinal cord lesion, and by clinical profile in the cerebellum lesion, but no reports with obvious CNS lesions like our patient through imaging methods. This is considered the first report of concurrent CNS and PNS lesions of the MAGAb-positive patient.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Anti-MAG antibody, axonal sensorimotor polyneuroopathy

Facilitated Subcutaneous Immunoglobulin 10% For CIDP: Effects Of Patient Factors On Serum Trough Immunoglobulin G

Poster No:
P 412

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Introduction:
The ADVANCE-CIDP 1 trial in chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) assessed the efficacy and safety of HyQvia, a facilitated subcutaneous immunoglobulin (fSCIG; Baxalta US, Inc., a Takeda company, MA, USA; immunoglobulin G [IgG] 10% with recombinant human hyaluronidase). This exploratory subgroup analysis evaluated the effects of intrinsic and extrinsic patient factors on serum trough total IgG levels.

Methods:
In the phase 3 ADVANCE-CIDP 1 study (NCT02549170), patients were randomized 1:1 to fSCIG or placebo for 6 months. Serum trough total IgG ($C_{trough\ IgG}$) levels were measured at baseline, interim, and study completion visits. Subgroup analyses examined categorical factors including age (≤55, >55 years), sex, body mass index (BMI; underweight, healthy, overweight, obese), race, dosing interval (every 2, 3, or 4 weeks), geographic region, presence of diabetes mellitus, and worsening of functional disability according to hand grip strength (≥8 kPa decrease in the more affected hand) or adjusted Inflammatory Neuropathy Cause and Treatment Disability score (≥1 point increase). Multiple pairwise comparisons were performed using Wilcoxon tests (significance level $p<0.05$).

Results:
In total, 132 patients (mean age 54.4 years, 43.9% female) received fSCIG (n=62) or placebo (n=70). In general, $C_{trough\ IgG}$ levels were significantly higher for fSCIG-treated patients than for those receiving placebo. $C_{trough\ IgG}$ levels were generally comparable among age, sex, and BMI subgroups. $C_{trough\ IgG}$ levels in subgroups without functional worsening were significantly higher with fSCIG than with placebo, but no significant differences in $C_{trough\ IgG}$ levels between fSCIG and placebo were observed in those with functional worsening.

Conclusions:
fSCIG treatment achieved higher $C_{trough\ IgG}$ levels compared with placebo across most patient factor subgroups. Higher $C_{trough\ IgG}$ levels were seen after fSCIG treatment in subgroups without functional worsening versus placebo, suggesting some correlation between serum trough IgG levels and clinical response. Study funder/writing support funder: Takeda Development Center Americas, Inc./Takeda Pharmaceuticals International AG

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: Study funder/writing support funder: Takeda Development Center Americas, Inc./Takeda Pharmaceuticals International AG.

Keywords: Chronic inflammatory demyelinating polyradiculoneuropathy, Facilitated subcutaneous immunoglobulin, Serum trough immunoglobulin G

Defining Schwann Cell – T Cell Interactions In Inflammatory Neuropathies By Nanoscale FIB-SEM 3D Imaging

Poster No:
P 413

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Institutions:
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Introduction:
Immune-mediated neuropathies such as the Guillain-Barré-Syndrome display infiltration of T-lymphocytes and macrophages in nerve biopsies. An emerging body of evidence indicates that Schwann cells can act as antigen presenting cells and therefore may feature immunocompetence. Here, we aim to examine the interaction between T-cells and Schwann cells by using high resolution electron microscopy to investigate the possible immunologically relevant nature of this contact, which could further represent a therapeutic target.

Methods:
Our approach utilizes a co-culture model of murine embryonal dorsal root ganglia sensory neurons and primary Schwann cells isolated from Lewis rats. Following at least 4 weeks of myelination, fully myelinated cultures were exposed to neuritogenic T-cells extracted from Lewis rats immunized with myelin protein 2 peptide (P255-78). Cultures were monitored by live cell bright-field microscopy to identify contact sites displaying interaction of cells. Focused ion beam scanning electron microscopy was used to trace the Schwann cell-T-cell contact in 3D at high resolution. Alternatively, cultures were used for immunostaining or supernatant was analyzed for inflammatory cytokines.

Results:
Interaction sites between T-cells and Schwann cells displayed cellular membrane regions of higher electron densities indicating recruitment of membrane bound molecules specifically limited to these contacts. In accordance to that, interaction sites showed accumulation of immunological relevant markers. Reconstructed 3D models showed the spatial size of contact sites in comparison to cell sizes.

Conclusions:
This combination of advanced cell culture techniques and state-of-the-art multimodal imaging approaches offers a deeper insight into the complex cellular mechanisms underlying myelin destruction seen in immune-mediated neuropathies. The morphological alterations of the T-cell, its stable bond to the Schwann cell and the seemingly activated binding site observed by electron microscopy and immunostaining indicate an immunologically relevant interaction. Deciphering the nature of this interaction requires further investigation in order to define its potential role in disease pathology.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: inflammatory neuropathies, Schwann cell, T cell, electron microscopy, Guillain-Barré-syndrome

Hemolytic Anemia Following Intravenous Immunoglobulin Administration In Guillain-Barré Syndrome – Experience From A Single Centre

Poster No:
P 414

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Introduction:
Intravenous immunoglobulin (IVIG) is an important treatment for many neuroinflammatory conditions, including Guillain-Barré syndrome (GBS). Hemolytic anemia (HA) occurs in approximately 1.6-6.7% of cases following IVIG (in both de novo and repeat exposure), within 2 weeks of administration; Sensitisation via passive transfusion of red blood cell isoagglutinins has been implicated. We report the incidence and clinical characteristics of GBS patients developing HA following IVIG exposure.

Methods:
We reviewed the case records of GBS patients presenting to our institution and identified those developing anemia following IVIG use. We assessed the onset of anemia from IVIG administration, mechanism (hemolytic or non-hemolytic), magnitude of hemoglobin reduction, and grade of anemia defined by National Cancer Institute Common Terminology Criteria for Adverse Events. We excluded patients with pre-existing hematological derangements, who did not receive IVIG, and/or those without serial hemoglobin assessment within 2 weeks following IVIG.

Results:
Of 54 GBS patients identified, 2 developed HA, both with B+ blood type: Patient 1 is a 75-year-old female developing Grade 3 anemia following a 3.5g/dL hemoglobin reduction 4 days into IVIG therapy, necessitating blood transfusion. Patient 2 is a 28-year-old female developing Grade 2 anemia following a 4.7g/dL hemoglobin reduction 1 day after completing IVIG. Patient 2 had infective symptoms that resolved 1 week before presentation; neither patient had active infection contemporaneous with anemia onset. No alternative cause of hemolysis or evidence of hemorrhage was identified. A further 8 patients had anemia with insufficient features to identify the causative process. Anemia occurred at mean 7 days (range 3-11) after IVIG administration, with mean hemoglobin reduction of 3.5 g/dL (range 2.2-5.1), resulting in Grade 2-3 anemia in 6.

Conclusions:
HA following IVIG is an infrequent but important adverse event, often occurring within 2 weeks of IVIG administration. Its largely self-limiting and benign course is reassuring and should not deter necessary treatment.

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Yes

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Grant Support:

Keywords: Guillain-Barre Syndrome, Hemolytic anemia, Intravenous Immunoglobulin, Adverse reaction

Antibodies against peripheral nerve antigens after mRNA COVID-19 vaccination

Poster No:
P 415

Authors:
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Institutions:
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Introduction:
The rapid spread of coronavirus disease 2019 (COVID-19) and the complications resulting from the disease have led to a rapid development of vaccines against SARS-Cov2. Neurological adverse events, including inflammatory neuropathies, often are a matter of concern in massive vaccination campaigns. As autoantibodies against peripheral nerve antigens are present in a proportion of patients with inflammatory neuropathies, the objective of this study is to analyse the appearance of antibodies against peripheral nerve antigens in patients following mRNA COVID-19 vaccination.

Methods:
Of a cohort of 454 patients included in a prospective observational study on immune humoral and T-cell responses after COVID-19 vaccination (390 with multiple sclerosis, and 64 with other inflammatory neurological disorders: 22 myasthenia gravis, 18 neuromyelitis optica spectrum disorder/MOG antibody-associated disease, 9 autoimmune encephalitis, 7 inflammatory neuropathies, 4 GAD-antibodies spectrum disorders, and 4 others); 444 (97.8%) received a mRNA COVID-19 vaccine. Antiganglioside (GM1, GD1b and GQ1b) and anti-nodo/paranodal antibodies (NF155, NF140, CNTN1 and CASPR1) were tested in 429 patients after vaccination. Moreover, serum reactivity patterns on monkey sciatic nerve sections were analysed in 100 patients. Sera were extracted before COVID-19 vaccination and 1 month after the second dose.

Results:
None of the patients included in the study presented antibodies against gangliosides or nodal/paranodal proteins. Anti-monkey peripheral nerve experiments revealed anti-nerve reactivity in 7 patients but these reactivities were already present in baseline samples (before vaccination). Experiments analysing staining patterns in monkey peripheral nerve of the remaining samples are undergoing.

Conclusions:
In patients with multiple sclerosis or other inflammatory neurological disorders the development of antibodies against the peripheral nerve is either rare or non-existent after mRNA COVID-19 vaccination.

References:
No

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References 2:

References 3:

References 4:

Grant Support:

Keywords: Antibodies, Vaccination

Comparative Effectiveness Of Imlifidase Added To Immunoglobulin Treatment In Guillain-Barré Syndrome: Study Protocol

Poster No:
P 416

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Institutions:
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Introduction:
Despite treatment with intravenous immunoglobulins (IVIg) or plasma exchange, patients with Guillain-Barré syndrome (GBS) can have a poor clinical outcome. About 25% deteriorate during treatment and 20% are still unable to walk independently 6 months after disease onset. Imlifidase is a promising novel treatment that rapidly cleaves immunoglobulin G and its safety and efficacy in GBS is currently being investigated in an open-label phase II trial. A protocol is proposed for a study that aims to compare the effectiveness of imlifidase added to standard IVIg treatment on outcome in GBS by using data of selected control patients from the International GBS Outcome Study (IGOS).

Methods:
IGOS is an observational international prospective cohort study that collects high quality and standardized data of 2000 patients, which has the potential to be used as a platform for comparative effectiveness research of new treatments. Control patients in IGOS will be selected by using the same eligibility criteria as used in the phase II trial and a propensity score based on the current validated clinical prognostic models for GBS at baseline. The propensity score represents the probability of a patient to be assigned to imlifidase treatment given baseline characteristics. Based on the propensity scores, each patient treated with imlifidase will be matched to up to four controls from IGOS. A comparative analysis will be conducted between the intervention and control group assessing disability, disease severity and recovery time.

Results:
Recruitment of patients in the phase II trial is ongoing. Final results are expected in 2024, when the outcome of approximately 30 patients treated with imlifidase will be compared with up to 120 matched control patients from IGOS.

Conclusions:
This comparative effectiveness study tries to emulate a randomized controlled trial and may provide initial evidence for imlifidase treatment in GBS.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Guillain-Barré syndrome, Comparative effectiveness research, Treatment, Imlifidase, Study Protocol

Development of a Video-Based Evaluation Test for Sweating Disorders.

Poster No:
P 417

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Introduction:
Small-fiber neuropathy is defined as a structural abnormality of small-nerve fibers with degeneration of the distal terminations of nerve endings. Peripheral autonomic nervous system dysfunction may be one of the earliest signs of small-fiber neuropathy. The gold standard for the early diagnosis of small-fiber dysfunction is skin biopsy, a method not widely available, both because of the high costs and the associated technical difficulties. Other methods for measuring sweating activity rely on expensive machines and are time-consuming. Aim: To devise a new method to measure the activity of sweat glands that can be used to allow the early diagnosis of small-fiber neuropathy.

Methods:
We have standardized a new, low-cost, easy-to-perform test to semi-qualitatively analyze the sweating activity by video recording the function of sweat glands on the volar surface of the index finger (0.5cm2) for 40 seconds. Recordings were made during resting state (20s) and during arm elevation, deep inspiration, and handgrip strength (20s). A digital microscope (optic zoom 1000x) was used to measure the sweat gland activity.

Results:
Results: Ethics research committee from our university hospital approved the study, and participants signed the informed consent. Thirty-five patients (19 women; mean age ±43.89) diagnosed with Familial Amyloid Polyneuropathy (PAF) and 20 healthy controls (11 women; mean age ±45.35) participated. Tests were performed in the mornings (08:00-11:00) to avoid circadian rhythm variations. We found clear differences on the sweating activity between groups during both rest and muscle contraction.

Conclusions:
Conclusion: This research presents a method to analyze the activity of sweat glands, in real time, along with muscle contraction. Here we show that video recording the activity of sweat glands in response to different muscle activities might be a useful tool to monitor the activity of the peripheral autonomic nervous system. The next step is to devise an application to better interpret the images.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Small-fiber neuropathy, sweating, Familial Amyloid Polyneuropathy

Understanding human peripheral neuropathies at single cell resolution

Poster No:
P 418

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Introduction:
Polyneuropathies (PNP) are common and disabling neurological diseases with many potential causes. Biopsies of the purely sensory sural nerve are the last step for diagnosing treatable forms of human PNP. However, analysis of these precious biological specimens is currently restricted to histology. We previously analyzed the cellular composition of peripheral nerves in rodents using single cell transcriptomics. We identified subtypes of endoneurial macrophages and a unique transcriptional response of Schwann cells to autoimmunity. We here translated the technology to human sural nerve biopsies.

Methods:
We performed single nuclei RNA-sequencing (snRNA-seq) of cryo-preserved human sural nerve biopsies from patients with immune-mediated and other PNPs.

Results:
After extensive optimization, we generated unbiased snRNA-seq data from cryo-preserved sural nerve biopsies. We confirm the composition of PNS cells previously described in rodents and identify a unique transcriptional signature of Schwann cells in inflammatory PNP. We also find preliminary evidence suggesting an intra-neural expansion of NK cells in chronic inflammatory PNP as previously reported in cerebrospinal fluid.

Conclusions:
Single cell transcriptomics has the potential to improve the understanding and diagnosis of polyneuropathies and suggests an involvement of NK cells in local inflammation.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: BMBF

Keywords: sural nerve biopsies, inflammatory neuropathies, single nuclei RNA-sequencing

Potential Clinical Relevance Of AChR Antibodies In Intravenous Immunoglobulin

Poster No:
P 419

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Introduction:
New, fatigable weakness in an individual patient with severe, longstanding CIDP following IVIg administration on multiple occasions with improvement after PLEX was observed. 17/20 serum samples had an AChR antibody titre above the laboratory positive threshold (0.45nmol/L). Mean (S.D.): 1.0 (0.3)nmol/L; range: 0.38-1.6nmol/L. Given the prevalence of AChR antibody positive myasthenia gravis is 150-200 cases per million in US and European populations we considered the possibility of (i) transmission of AChR antibodies to patients receiving intravenous immunoglobulin (IVIg) as maintenance treatment for inflammatory neuropathy and (ii) the potential for clinical effect. This study aimed to establish AChR titres in a range of therapeutic IVIg preparations and post-infusion 'seropositivity' and/ or clinical manifestation in a random sample of inflammatory neuropathy patients on maintenance IVIg treatment.

Methods:
AChR antibody titres were tested in by ELISA as per standard practice in the neuroimmunology laboratory. Samples were collected from IVIg batches with corresponding post-infusion serum samples from a randomly selection of patients from the inflammatory neuropathy cohort. Case note review for evidence of clinical relevance was performed. Patch clamp examination of AChR activity on exposure to antibody positive IVIg samples is pending.

Results:
20 samples from 17 batches of IVIg preparations in clinical use were collected (Privigen, Flebogamma Dif, Intratect, Octagam, Iqymune, Gamunex). All IVIg samples tested had detectable levels of AChR antibodies. Mean (S.D.) titre was 2.2nmol/l (2.4), range: 0.21-9.4nmol/l. Mean (S.D.) mass of AChR antibodies in IVIG doses administered was 593ng (610), range: 33.3-2278ng. No post-infusion patient sera were positive. No clinical manifestations of myasthenia gravis were observed in this group.

Conclusions:
Although detectable levels AChR antibodies were found in therapeutic IVIg samples this did not result in clinically significant levels in patient serum or clinical manifestation in this small study. Molecular studies to explore potential for clinical impact are pending.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Immunoglobulin, Acetylcholine receptor antibody

INCbase: the Global CIDP Registry – an Update

Poster No:
P 420

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Introduction:
INCbase is a global web-based registry, with the collective aim of gathering large-scale uniform, high quality prospective data on CIDP patients. Objectives include development of a prognostic model to predict treatment response and discovery of novel biomarkers for diagnosis, disease activity and prognosis, and to elucidate unknown pathophysiological aspects of CIDP.

Methods:
Comprehensive baseline data is collected, with follow-up varying from a minimal dataset each 6 months (core module) to more extensive data collection and extra visits (extended module). In January 2023, the home assessment module was introduced, enabling close monitoring of patients starting treatment withdrawal. Supplementary modules capture data on plasma-exchange and subcutaneous immunoglobulins. Biomaterial collection (optional) will facilitate the identification of novel biomarkers. Recent database adjustments incorporate additional patient specific impairment measures, updated EAN/PNS 2021 diagnostic criteria, and automated collection of home assessment data.

Results:
As of January 11th 2023, 22 centers from eight countries are operational, with a total of 127 patients enrolled. Around 20-30 additional centers are expected to complete local regulatory procedure in the near future, including facilities in Australia, Belgium, Denmark, Germany, India, Spain, the UK and the US.

Conclusions:
Conclusions Collection of large-scale standardized prospective data on CIDP patients is feasible using INCbase. Future perspectives include incorporation of platform trials infrastructure and crosstalk with other CIDP databases. Further enrollment of centers and patients is anticipated. Centers are invited to contact us for participation. Collected data will be used to answer vital unresolved questions in CIDP. INCbase is supported by the GBS/CIDP foundation, CSL Behring, Grifols, Takeda, Kedrion and Terumo BCT.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: INCbase, cidp, registry, inflammatory, neuropathy

Autophagy Regulation in Peripheral Blood Mononuclear Cells of Patients with Chronic Inflammatory Demyelinating Polyneuropathy

Poster No:
P 421

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Introduction:
Chronic inflammatory demyelinating polyneuropathy (CIDP) is rare immune-mediated peripheral polyneuropathies with unknown etiopathogenesis. The intracellular energy sensor AMP-activated protein kinase (AMPK) and master metabolic regulator the mechanistic target of rapamycin (mTOR) regulate immune cell function through various mechanisms, including autophagy.

Methods:
We analyzed AMPK activation status and expression of genes involved in autophagy regulation in peripheral blood mononuclear cells of CIDP patients at transcriptional level, as well as their correlation with the severity of the disease. The study included 18 drug-naïve CIDP and 21 age/sex-matched healthy control subjects (HC). The activation status of AMPK in PBMC was assessed by immunoblot, while the expression of mRNA for autophagy regulators Forkhead Box O1 (FOXO1), FOXO3B, Autophagy related 5 (Atg5), Atg7, Beclin-1 and Microtubule-associated protein 1 light chain 3B (LC3B) was analyzed by RT-qPCR.

Results:
Our results demonstrate upregulation of transcription factor FOXO3B, Beclin-1 and Atg7 in CIDP. By contrast, FOXO1 and Atg5 mRNA expression was downregulated. LC3B mRNA and AMPK protein levels were similar in CIDP patients and HC. FOXO3B and LC3 mRNA levels significantly correlated with Inflammatory Neuropathy Cause and Treatment (INCAT) Disability Score. We did not identify statistically significant correlations of mRNA levels with Medical Research Council (MRC) Sum Score.

Conclusions:
These findings warrant further clarification of the role of autophagy-related mediators in CIDP pathogenesis and/or progression.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: The study was supported by an unrestricted grant from Kedrion Biopharma (Castelvecchio Pascoli, Italy), Ministry of Education, Science and Technological Development of the Republic of Serbia (Contract No. 451-03-9/2021-14/200110), and Serbian Society for

Keywords: chronic inflammatory demyelinating polyneuropathy, autophagy, AMP-activated protein kinase, forkhead box O3B

Therapeutic outcomes and electrophysiological biomarkers in anti-MAG neuropathy: a multicenter cohort study in Korea

Poster No:
P 422

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Introduction:
Anti-myelin-associated glycoprotein (MAG) neuropathy is a distal, sensory-dominant demyelinating neuropathy mediated by anti-MAG antibodies. Unlike other immune-mediated neuropathies, anti-MAG neuropathy is often refractory to various immunotherapies. Therefore, it is important to identify relatively effective treatment options and develop novel biomarkers to facilitate future trials.

Methods:
Ninety-one patients with high anti-MAG antibody titers were recruited from seven tertiary hospitals in South Korea. Twenty-three false-positive cases were excluded, and the baseline features, therapeutic outcomes, and nerve conduction study (NCS) findings of 68 patients were analyzed.

Results:
Fifty patients (73.5%) received a total of 96 lines of immunotherapy. The rate of positive responses was highest among patients treated with zanubrutinib (50%) and rituximab (36.4%), followed by corticosteroids (17%), immunosuppressants (9.5%), intravenous immunoglobulin (5%), and plasma exchange (0%). Disability and weakness were significantly associated with multiple NCS parameters. Average distal compound muscle action potential amplitudes were longitudinally correlated with clinical changes, with a 16.2 percentile decrease being identified as an optimal cut-off for predicting clinical exacerbation (AUC : 0.792).

Conclusions:
Our study supports the use of NCS as an objective marker for estimating disease burden and for tracking clinical changes in patients with anti-MAG neuropathy. We report the beneficial effects of rituximab and a new drug, zanubrutinib, compared to conventional immunotherapies.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Anti-MAG neuropathy, Electrophysiology, Cohort

Japan Neuro-immunology Association study: CIDP registry

Poster No:
P 423

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Introduction:
Patient registries are a useful and powerful tool for studying the pathogenesis, clinical profile, and prognosis of rare diseases. To facilitate epidemiological studies and drug development for neuroimmunological diseases, we have established the patient registries in association with the Japanese Society of Neuroimmunology.

Methods:
First, we have initiated the CIDP registry, which enrolls patients with CIDP, anti-MAG neuropathy, and multifocal motor neuropathy to obtain data on clinical profile, electrodiagnosis, and treatment response, as well as biosamples at baseline. Follow-up will be performed annually.

Results:
To date, 90 CIDP patients have been enrolled in the registry, and the current target number of cases is 500. Additional longitudinal observational studies can be conducted in enrolled patients to investigate the real-world efficacy and safety of recently launched drugs for a period every few months. Cross-sectional surveys of electronic patient-reported outcomes can also be conducted in a timely manner. In addition, the registry can be used as a trial readiness cohort for ongoing and future clinical trials.

Conclusions:
We also intend to use it for post-marketing surveillance of newly approved drugs. In the future, molecularly targeted drugs will be developed for each subtype of CIDP. At that time, the number of patients with each subtype of CIDP will be extremely small, and it will be very difficult to determine the efficacy and safety of molecularly targeted drugs in randomized controlled trials, so ideally, the cases in this registry will be used as historical controls in new drug applications. We have now begun building a registry for neuromyelitis optica and plan to expand the registry to include multiple sclerosis, myasthenia gravis, and autoimmune encephalitis in the future.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: Investigator initiated study funded by CSL Behring

Keywords: registry, CIDP, epidemiology, drug development

A Deep Learning Approach To Motor Unit Number Estimation In Chronic Inflammatory Demyelinating Neuropathy

Poster No:
P 424

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Introduction:
Axonal degeneration is the primary cause of motor function impairment in chronic inflammatory demyelinating neuropathy (CIDP). The decrease in the maximal compound muscle action potential (CMAP) is a limited measure of axonal loss due to collateral sprouting. Additional information could be obtained by recording the CMAP responses for a range of stimuli of increasing intensity, referred to as a muscle scan (MScan). We propose a novel motor unit number estimation (MUNE) method from MScan, referred to as EXMUNE, which is based on a deep neuronal network trained to account for changes in motor unit excitability that can occur in CIDP.

Methods:
MScanFit [1] introduced a simplified MScan model characterizing each motor unit by its amplitude, threshold, as well as threshold variability, a measure of axonal excitability. By varying all the model parameters, we generated 100,000 simulated MScans, in the form of grayscale density images. This simulated dataset with known number of motor units was used as ground truth for training a deep convolutional network, using a Visual Geometry Group type architecture terminating with a regression layer. We compared MScanFit MUNE and EXMUNE on real MScan recordings collected by stimulating the median nerve at wrist and recording the CMAP over the abductor pollicis brevis muscle.

Results:
We found that in a group of healthy volunteers, the EXMUNE was largely similar to the MScanFit MUNE. Nevertheless, at single CIDP patient level, the EXMUNE - detected axonal loss was more concordant with degeneration detected by conventional needle electromyography.

Conclusions:
Our data suggest that deep learning can improve MUNE from MScan in CIDP. Given that an MScan can be recorded within 10-minutes in continuation of the conventional conduction studies and that the proposed image regression works in seconds, without user-dependent parameters, EXMUNE could become an attractive clinical biomarker of axonal loss in neuropathy.

References:
Yes

References 1:
Bostock, H., Estimating motor unit numbers from a CMAP scan. Muscle Nerve, 2016. 53(6): p. 889-96.

References 2:

References 3:

References 4:

Grant Support: The project was supported by the Jytte and Kaj Dahlboms Foundation and the Danish Society for ALS.

Keywords: MUNE, CIDP, deep learning, MScanFit, EMG

Anti-AGO1 antibodies identify a distinctive subgroup of sensory neuronopathy

Poster No:
P 425

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Introduction:
Autoantibodies (Abs) improve diagnosis and treatment decisions of idiopathic neurological disorders. Recently, Abs against Argonaute proteins (AGO) were suggested as potential autoimmunity biomarkers in neurological disorders [1]. Here, we aim to reveal 1) the frequency of AGO1 Abs in sensory neuronopathy (SNN), 2) titers and IgG subclasses, and 3) their clinical pattern including response to treatment.

Methods:
This retrospective multicentric case/control study screened 132 patients with SNN, 301 with non-SNN neuropathies, 274 with autoimmune diseases (AID), and 116 healthy controls (HC) for AGO1 Abs via conformation-stabilizing ELISA [2]. Seropositive cases were also tested for IgG subclasses, titers, and conformation specificity.

Results:
AGO1 Abs occurred in 44 patients, comprising significantly more SNN [17/132 (12.9%)] than non-SNN neuropathies [11/301 (3.7%); $p = 0.001$], AID [16/274 (5.8%); $p = 0.02$], or HC [0/116; $p < 0.0001$]. Abs titers ranged from 1:100 to – 1:100,000. IgG subclass was mainly IgG1, and 11/17 AGO1 Abs-positive SNN (65%) had a conformational epitope. AGO1 Abs-positive SNN was more severe (e.g., SNN score: 12.2 vs. 11.0, $p = 0.004$) and they more frequently and more efficiently responded to immunomodulatory treatments than AGO1 Abs-negative SNN (7/13 [54%] vs. 6/37 [16%], $p = 0.02$). Regarding the type of treatments more precisely, this significant difference was confirmed for the use of intravenous immunoglobulins (IVIg) but not for steroids or second line treatments. Multivariate logistic regression adjusted for potential confounders showed that AGO1 Abs-positivity was the only predictor of response to treatment (OR 4.93, 1.10-22.24 95% CI, $p = 0.03$).

Conclusions:
Although AGO Abs are not specific for SNN, based on our retrospective data they may identify a subset of SNN cases with more severe features and a possibly better response to IVIg. The significance of AGO1 Abs in clinical practice needs to be explored in a larger series.

References:
Yes

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Do LD, Moritz CP, Muñiz-Castrillo S, Pinto AL, Tholance Y, Brugiere S, Couté Y, Stoevesandt O, Taussig MJ, Rogemond V, Vogrig A, Joubert B, Ferraud K, Camdessanché JP, Antoine JC, Honnorat J. Argonaute Autoantibodies as Biomarkers in Autoimmune Neurologic

References 2:
Conformation-stabilizing ELISA and cell-based assays reveal patient subgroups targeting three different epitopes of AGO1 antibodies. Front Immunol. 2022 Oct 20;13:972161. doi: 10.3389/fimmu.2022.972161. PMID: 36341350; PMCID: PMC9630334.

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References 4:

Grant Support: 1) BETPSY project, French National Research Agency (ANR), ANR-18-RHUS-0012; 2) FRM (Fondation pour la Recherche Médicale), DQ20170336751. 3) Association Française contre les Myopathies, AFM-MyoNeurALP project 6.1.1 4) Fonds de dotation CSL Behring pour

Keywords: Argonaute antibodies, Sensory neuronopathy, Anti-Su antibodies, Diagnosis, Treatment prediction

The antibody repertoire of inflammatory sensory neuronopathies targets pathways of the innate and adaptative immune system.

Poster No:
P 426

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Introduction:
Dysimmune sensory neuronopathies (SNN) can be paraneoplastic while others occur with systemic autoimmune diseases (e.g., Sjögren syndrome) or remain isolated. Antibodies (AB) occur in paraneoplastic (anti-Hu AB) and non-paraneoplastic SNN (anti-FGFR3 AB), but the disease pathophysiology is unknown. Recent evidences indicate that AB targeting immune system proteins are produced during autoimmune diseases. Systemic approaches addressing the entire antibody repertoire promise a comprehensive understanding of immune disease mechanisms [1].

Methods:
We systematically analyzed the dysimmune SNN AB repertoire against immune system pathways with two protein arrays. Array-type-1 covering 7,634 human proteins was used with 38 SNN (16 with non-paraneoplastic dysimmune SNN comprising 7 with, 9 without anti-FGFR3 AB; 8 with paraneoplastic SNN and anti-Hu AB; 14 controls comprising 7 other neuropathies, 7 healthy controls [HC]). Array-type-2 covering 15,797 human proteins was used to test 43 subjects (12 with non-paraneoplastic dysimmune SNN and no AB; 31 controls comprising 22 other neuropathies, 9 HC). We performed overrepresentation analyses with the immune-system-related proteins via Reactome and PantherDB. Serum INF alpha-2, IFN-gamma, IL 1-beta, IL6, IL17, and TNF alpha were measured by Bio-Plex ProTM Reagent Kit III.

Results:
Dysimmune SNN sera interacted with a significantly higher number of proteins of immune system pathways than other study groups. More pathways of the innate immune system, adaptative immune system, and cytokine signaling system were overrepresented in dysimmune SNN than in HC, anti-FGFR3-neagtive SNN, or paraneoplastic SNN. Anti-FGFR3-positive SNN were more reactive with immune system proteins than anti-FGFR3-negative patients, both regarding the number of targeted proteins and overrepresented pathways. Cytokine levels were higher in anti-FGFR3-negative than -positive patients for IFN alpha-2 and TNF alpha.

Conclusions:
The antibody repertoire of non-paraneoplastic SNN may be an imprint of disease-relevant immunological pathways. The identified repertoires of targeted antigens involve cytokine signaling pathways that may also contribute to the pathogenesis of Sjögren Syndrome.

References:
Yes

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Moritz CP, Paul S, Stoevesandt O, Tholance Y, Camdessanché JP, Antoine JC. Autoantigenomics: Holistic characterization of autoantigen repertoires for a better understanding of autoimmune diseases. Autoimmun Rev. 2020 Feb;19(2):102450. doi: 10.1016/j.autre

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Grant Support: 1) University Hospital of Saint-Etienne; 2) German Research Foundation (DFG; MO 3240/1-1:1); 3) Association Française contre les Myopathies (AFM-MyoNeurALP project 6.1.1); 4) BETPSY project, Investissements d'Avenir program of the French National Resea

Keywords: Autoantigenomics, Sensory neuronopathy, Antibody repertoire, Immune system pathways, Sjögren syndrome

A case of acute conduction block neuropathy after dengue infection.

Poster No:
P 427

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Introduction:
Guillain-Barré syndrome (GBS) is an immune mediated disorder targeting the peripheral nerves. Variants of GBS described include Acute inflammatory demyelinating neuropathy (AIDP), Acute motor axonal neuropathy (AMAN), Acute motor and sensory neuropathy (AMSAN) and Miller- Fisher syndrome. Conduction block is the hallmark of demyelinating neuropathies. However, reversible conduction failure from paranodopathy has been recognized as another mechanism of conduction block in axonal forms of GBS. Upper respiratory and gastro-intestinal infections usually precede the neurological symptoms (in about 60 % of cases).

Methods:
We describe a case of acute motor conduction block variant of GBS that followed recent Dengue infection.

Results:
A 28-year-old man presented with progressive weakness, initially starting in the lower limbs, that progressed to upper limbs over 6 days. He had no bulbar, facial or extra-ocular muscle weakness or numbness. The patient had recovered 10 days ago from dengue infection. Nerve conduction study (NCS) showed conduction blocks in bilateral median, ulnar, tibial and peroneal nerves. Distal latency, F latency and conduction velocities were normal. Sensory NCS studies were normal. The patient underwent 7 cycles of plasma exchange. His weakness improved mildly. A follow-up nerve conduction studies after 12 days showed severely reduced to non-recordable CMAPs. However, there were no signs of demyelination. Anti-ganglioside antibodies were negative. The patient received 120 gm of intravenous immunoglobulins over 5 days. He improved. On last follow-up, 1 month post-treatment, he was able to stand with the help of support, lower limb power was grade 2 to 3.

Conclusions:
Acute conduction block neuropathy variant of GBS can follow Dengue infections.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: Nil

Keywords: inflammatory neuropathy, dengue infection, Guillain-Barré syndrome

Clinical significance of the nerve enlargement in chronic inflammatory demyelinating polyradiculoneuropathy

Poster No:
P 429

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Introduction:
The 2021 guideline of the EAN/PNS on chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) includes nerve enlargement detected by nerve ultrasound as a supportive criterion. The aim of the study was to elucidate the validity of nerve ultrasound criteria proposed by the EAN/PNS guideline and to identify the clinical and pathological significance of nerve enlargement in treatment-naïve CIDP patients.

Methods:
We enrolled 15 consecutive CIDP patients who met the 2021 EAN/PNS electrodiagnostic criteria. All patients underwent clinical and nerve ultrasound evaluation prior to initiating therapy and subsequently responded to the immune treatment. First, we calculate the proportion of CIDP patients who met the ultrasound criteria. Second, a correlation between the nerve cross-sectional area (at the forearm and upper arm of the median nerve and C6 nerve root) and clinical parameters (disease duration, cerebrospinal fluid (CSF) protein level, Overall Neuropathy Limitations Scale（ONLS）and its change six months after the initiation of treatment) was analyzed.

Results:
CIDP patients consisted of 11 typical, three distal, and one multifocal CIDP patients. Seven patients (67%) met the ultrasound criteria of the EAN/PNS guideline. CSA of the median nerve at the forearm positively correlated with the disease duration ($p = 0.026$) and CSF protein ($P = 0.032$). In addition, both the CSA of the C6 root and the sum of the CSAs at three sites correlated with the CSF protein level ($p = 0.044$ and $p = 0.020$, respectively).

Conclusions:
One-third of patients who met the electrodiagnostic criteria did not meet the ultrasound criteria. The correlation between nerve CSA and CSA protein level may indicate that the degree of nerve enlargement reflects the disease activity, although no correlation was detected between nerve CSA and disease severity (ONLS).

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: CIDP, ultrasound

Epitope mapping of anti-neurofascin 155 antibodies in a large cohort of autoimmune nodopathy

Poster No:
P 430

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Introduction:
Autoantibodies against cell adhesion molecules located in nodes of Ranvier and paranodal regions, including neurofascin 155 (NF155), have been discovered in subsets of patients with chronic inflammatory demyelinating polyneuropathy. NF155 consists of six immunoglobulin domains, four fibronectin type III (Fn) domains, a transmembrane domain, and a short cytoplasmic domain. Neurofascin 186 (NF186), a nodal isoform of NF155, lacks the third Fn3 domain (Fn3), instead having a mucin domain between the fourth Fn (Fn4) and the fifth Fn domain. Although several epitope mapping studies for anti-NF155 antibodies have been published, their results contain some contradictions. The aim of this study is to identify the epitopes of autoantibodies against NF155 in a large cohort of patients with anti-NF155 antibody-positive (NF155+) autoimmune nodopathy (AN).

Methods:
Human Embryonic Kidney cells 293 cells stably expressing NF155, NF186, third and fourth fibronectin domains (Fn3-Fn4) within NF155 and those transiently expressing Fn3, Fn4, and shorter Fn3-Fn4 domains of NF155 were developed. Immunoblotting assays and flow cytometric cell-based assay (CBA) were performed to determine the expression of each protein and identify the target epitopes in the serum samples from 100 IgG4 NF155+ and four non-IgG4 NF155+ patients and eight healthy controls.

Results:
The expression of NF186, NF155, Fn3-Fn4, and other truncation variants of NF155 were confirmed by both western blot and flow cytometric CBA. Flow cytometric CBA showed that autoantibodies in all of 104 NF155+ patients bound to Fn3-Fn4. None were reactive to NF186, Fn4 and shorter Fn3-Fn4, while only one IgG4 NF155+ patient (1.0%) was reactive to Fn3 in addition to Fn3-Fn4. Western blot utilizing representative samples, generally reproduced the results of CBA.

Conclusions:
Our present study among a large cohort clarified that the primary epitope of anti-NF155 antibodies is located in Fn3-Fn4 domain but not Fn3 or Fn4 domain.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: This study was supported by the Japan Agency for Medical Research and Development (AMED), Grant Number JP20ek0109376 and the Moonshot Research and Development Program (JP21zf0127004) from AMED, and by the Japan Society for the Promotion of Science (JSPS)

Keywords: epitope, neurofascin 155, autoimmune nodopathy, Nodes of Ranvier, antoantibody

Excellent response to anti-CD38 therapy with Daratumumab in a patient with severe refractory CANOMAD

Poster No:
P 431

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Introduction:
CANOMAD is the acronym for Chronic Ataxic Neuropathy, Ophthalmoplegia, IgM-paraprotein, cold Agglutinins, and anti-Disialosyl antibodies(1). Its main clinical features are chronic sensory ataxia and ophthalmoparesis, but a few patients may present a severe phenotype with muscular and bulbar weakness. One third associates hematologic malignancies, mainly Waldenström's macroglobulinemia (WM). IVIG and Rituximab have been proposed as the first and second-line treatments, but a recent study reported an overall clinical response less than 50%(2). New anti-CD38 mAb Daratumumab, targeting long-lived plasma cells and approved for the treatment of multiple myeloma, has recently been reported as a promising rescue therapy for treatment-refractory antibody-mediated neurological disorders(3).

Methods:
Here we report the first case of a very severe treatment-refractory CANOMAD, successfully treated with Daratumumab.

Results:
Case Presentation: A 69-year-old male presented with bilateral hand and foot paresthesias in 2018. In December 2021, he relapsed with gait ataxia, ophthalmoparesis, ptosis, facial weakness, dysphonia and tetraparesis. Neurophysiological studies showed a sensory-motor demyelinating polyneuropathy. IgM-kappa M-protein(<1g/L), IgM anti-disialosyl antibodies (at very high titers) and cold agglutinins were detected. Bone marrow aspiration detected lymphoplasmacytic cell infiltration. He was diagnosed with CANOMAD and, due to poor treatment response to IVIG, oral Prednisone and Rituximab, he was referred to our center in May 2022, where he presented with respiratory failure. Plasma exchange and Ibrutinib were initiated and tetraparesis and ventilatory function improved. However, after 1 month he remained plasma exchange-dependent to maintain the ventilatory function; Ibrutinib was discontinued and Daratumumab started in July 2022. After 3 doses, plasma exchange was discontinued and, since then, the patient showed a remarkable improvement. He is currently in clinical remission under monthly Daratumumab.

Conclusions:

Our observations suggest that anti-CD38 therapies may be an effective rescue treatment in patients with aggressive, treatment-refractory CANOMAD. Larger studies are needed to confirm the efficacy of anti-CD38 therapies in IgM antibodies-mediated neuropathies.

References:
Yes

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References 4:

Grant Support:

Keywords: CANOMAD, Daratumumab, Anti-CD38

GAMMAGARD LIQUID for the Treatment of Relapse in Chronic Inflammatory Demyelinating Polyradiculoneuropathy

Poster No:
P 432

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Introduction:
ADVANCE-CIDP 1 Epoch-2 evaluated efficacy and safety of GAMMAGARD LIQUID (GGL; intravenous immune globulin G infusion 10% [human]; Baxalta US, Inc., a Takeda company, MA, USA) in patients with chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) who relapsed during treatment with facilitated subcutaneous immunoglobulin (fSCIG) 10% or placebo.

Methods:
ADVANCE-CIDP 1 (NCT02549170), a Phase 3 randomized, placebo-controlled study assessing fSCIG 10% efficacy and safety, comprised two epochs. To enter open-label Epoch-2, eligible adults had confirmed CIDP relapse (≥1-point increase in adjusted Inflammatory Neuropathy Cause and Treatment [INCAT] disability scores from pretreatment baseline) during Epoch-1. Patients received loading GGL doses (2 g/kg) followed by maintenance infusions for 6 months. Outcomes included responder rate (proportion of patients with ≥1-point decrease in adjusted INCAT scores at treatment cessation versus pre-GGL baseline) and clinically meaningful improvement in functional ability, comprising either a ≥1-point decrease in adjusted INCAT scores, ≥8 kPa increase in grip strength (in the more affected hand), or ≥4-point increase in Rasch-built Overall Disability Scale (R-ODS) scores at study completion versus pre-GGL baseline. Median time to functional improvement (≥1-point decrease in adjusted INCAT scores versus pre-GGL baseline), patient-reported and health-related quality of life (HRQoL) outcomes and treatment-emergent adverse events (TEAEs) were also assessed.

Results:
Overall, 20 patients (mean age 50.9 years, 45.0% male) received GGL. Responder rate (95% CI) was 95.0% (83.2–100.0%). All patients (100%) achieved clinically meaningful improvement in functional ability. Mean change in adjusted INCAT scores was -2.0 points and median time to functional improvement was 25 days. Other functional, patient-reported and HRQoL outcomes supported GGL

efficacy. Overall, 14 patients (70.0%) experienced TEAEs, and no serious TEAEs or deaths were reported.

Conclusions:
GGL effectively treated CIDP relapse, achieving a 95% response rate, and improved functional ability with a favorable safety profile. Study funder/writing support funder: Takeda Development Center Americas, Inc./ Takeda Pharmaceuticals International AG.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: Study funder/writing support funder: Takeda Development Center Americas, Inc./ Takeda Pharmaceuticals International AG.

Keywords: Chronic inflammatory demyelinating polyradiculoneuropathy, Efficacy, Intravenous immunoglobulin, Phase 3 clinical trial, Safety

Clinical spectrum and outcomes of autonomic dysfunction in Guillain–Barré Syndrome: a prospective cohort study

Poster No:
P 433

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Introduction:
Autonomic dysfunction (AD) is a common feature of Guillain-Barré syndrome (GBS) and are associated with significant morbidity and mortality. Limited study evaluated the prevalence and impact of AD in GBS. We aimed to evaluate clinical spectrum, factors and outcome of GBS patients with AD at different time points of disease course.

Methods:
We prospectively enrolled GBS patients (N=748) from three cohort studies in Bangladesh. Clinical, and serological data were collected at enrollment, week-2, week-4 and week-26. AD was defined as any abnormalities in cardiac features (tachycardia/bradycardia/arrythmia); blood pressure (hypertension/hypotension/fluctuation), bowel-bladder involvement and pupillary-dysfunction. Differences between groups, survival and risk factors were analyzed by χ^2 test, Kaplan–Meir and logistic regression respectively.

Results:
Median age of the patients was 30 years with 67% male. Out of 748, 188 patients (25%) had AD mostly cardiac (15%) and blood pressure abnormalities (15%). AD was significantly associated with age; preceding respiratory tract infection; cranial nerve involvement; sensory deficit; MRC sum score; C. jejuni serology; and GM1 IgG antibody. At enrollment, mean serum neutrophil count, aspartate aminotransferase, and c-reactive protein were significantly higher whereas hemoglobin, and serum albumin were significantly lower among AD patients compared to non-AD patients. AD patients had higher proportion of mechanical ventilation (55% vs. 14%), mortality (35% vs. 8%), and poor outcome (GBS DS>2) at week-4 (83% vs. 60%) and week-26 (51% vs. 21%) than non-AD patients. Kaplan–Meir showed AD patients required longer time to regain independent locomotion than non-AD patients (log-rank test, P<0.016). Multivariate regression found higher neutrophil count as risk factor of poor outcome at week-26 among the AD patients (AOR: 1.92; 95%CI=1.04-3.53, p=0.037).

Conclusions:
AD is a manifestation of severe presentation and poor outcome of GBS. Systematic evaluation of AD is crucial to identify patients at risk of poor outcome and ensure integrative management of GBS.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: icddr,b, GBS CIDP Foundation International and NIH, USA

Keywords: Guillain–Barré Syndrome, autonomic dysfunction , Clinical spectrum , outcomes

Clinical practice and management of Guillain–Barré syndrome: a low- and middle-income country scenario

Poster No:
P 434

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Introduction:
Considerable variations in clinical practice for management of Guillain–Barré syndrome (GBS) has been observed worldwide. Diagnosis and treatment are challenging in low- and middle-income countries (LMIC) due to lack of facilities and low per-capita income. We aimed to evaluate the clinical practice, limitations and to provide future recommendation for GBS management in low resource settings.

Methods:
We conducted an explanatory-sequential mixed-methods survey among the neurologists and internists working in tertiary and secondary level government hospitals in Bangladesh. It had two independent phases: (i) Quantitative (cross-sectional survey to evaluate clinical practice and limitations); and (ii) Qualitative (key informant interview to explain certain clinical practice and provide future recommendations). Data were analyzed by frequencies and chi-square test (quantitative data neurologist vs. internist) and thematic analysis (qualitative).

Results:
A total of 159 physicians (65 neurologists and 94 internists) completed the quantitative survey. During diagnosis, 17% physicians followed established diagnostic criteria for GBS. Specific protocols for monitoring and treatment of GBS were used only by 12% physicians. Overcrowding of patients at all levels of hospitals, inadequate diagnostic facilities (CSF study and NCS), high cost and limited availability of standard therapy, inadequate logistics and trained personnel for ICU and rehabilitation services and lack of referral system were considered as major challenges for GBS management. To ensure early diagnosis and evidence-based treatments, qualitative respondents emphasized on regular and adequate trainings for health care providers involved in GBS management, development of cost-effective treatment strategies and appropriate guideline considering service delivery and socio-economic status of the country.

Conclusions:
Resource limitations contributed significant challenges for management of GBS in Bangladesh. Current study design and recommendations might be applied in other resource limited settings. Such data can assist the policy makers to identify areas that need urgent attention and effectively develop guideline to provide required services for GBS patients in LMIC.

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References 3:

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Grant Support: Incepta Pharmaceuticals, Bangladesh

Keywords: Guillain–Barré Syndrome, Clinical practice , low- and middle-income country

Baseline Muscle Strength Informs Patient Selection, Stratification, and Endpoints for a Pivotal, Randomized, Double-Blind GBS Study

Poster No:
P 435

Authors:
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Introduction:
Guillain-Barré syndrome (GBS) is an antibody-mediated autoimmune disease, characterized by peripheral nerve damage mediated by classical complement pathway activation. During GBS, recovering muscle strength precedes an improvement in function. ANX005 is a humanized monoclonal antibody targeting C1q, resulting in complement inhibition. Studies relating baseline characteristics prognostic to outcome are needed for clinical trial design.

Methods:
Cluster analysis was used post-hoc to evaluate the effect of baseline muscle strength on outcomes in two GBS studies: GBS-01 (N=50), a randomized placebo-controlled study of escalating doses of ANX005, and GBS-03 (N=14), a drug-drug interaction study of a single dose of ANX005 with IVIg (0.4 g/kg/day × 5 days).

Results:
Cluster analysis showed that baseline MRC-sum score, ≤20 and >20, had the greatest effect on outcome prediction. In GBS-01, 34 patients (68%) had baseline MRC ≤20 (range 0-20), and in GBS-03, 7 patients (50%) had baseline MRC ≤20 (range 0-20). In GBS-01, 16 patients (32%) had baseline MRC >20 (range 21-44), and in GBS-03, 7 patients (50%) had baseline MRC >20 (range 30-48). The average MRC scores at week 8 with MRC ≤20 and MRC >20 were 29 and 46, respectively, for GBS-01 patients and 20 and 54, respectively, for GBS-03 patients. For both GBS-01 and GBS-03 at week 8, 19/23 (82.6%) patients with baseline MRC >20 were able to walk independently or better (GBS-DS ≤2). Four patients did not improve or had a GBS-DS ≥3. In patients with baseline MRC ≤20, 8/41 (19.5%) patients reached GBS-DS ≤2.

Conclusions:
Using 2 clusters of baseline MRC scores (MRC scores ≤20 and >20), muscle strength appears to be prognostic for functional outcome 8 weeks after start of immunotherapy. The association between patient baseline MRC scores and GBS-DS outcomes have informed stratification and analysis of the primary endpoint for the ongoing pivotal study with ANX005, an anti-C1q therapy (NCT04701164).

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: Supported by Annexon Biosciences

Keywords: Guillain-Barré syndrome, complement, ANX005, outcomes

Demonstrating A Test Battery That Ensures Dose-Response Adjustment To Immunoglobulin Treatment In Patients With CIDP

Poster No:
P 436

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Introduction:
Chronic inflammatory demyelinating polyneuropathy (CIDP) is an immune-mediated disease which can be treated with immunoglobulin (IgG), steroids and plasma-exchange. In our settings IgG-treatment is first choice. Since CIDP disease activity may go into spontaneous remission, it is recommended that IgG response is tested every year. Since patients with CIDP may lose ambulation or hand function if they still have active disease, physicians are reluctant when it comes to tapering down successful IgG-treatment even after years of stable disease course in CIDP patients. In the present study, we present a taper-down strategy and a test battery that can be used for dose-response assessment in patients with CIDP treated with IgG.

Methods:
In this prospective observational study, we used gradual dose reduction (by 25% every 6 weeks) of IgG-treatment until relapse or discontinuation to identify IgG responders. To ensure that patients remained stable a physiotherapist evaluated muscle strength (isokinetic dynamometry, hand-held dynamometry and grip strength), physical function (Nine-Hole-Peg-Test, Six-Spot-Step-Test, 10-Meter-Walk-Test, 6-Minute-Walk-Test and Timed-Up-and-Go Test) and patient reported outcomes (EQ-5D-5L and INCAT) at baseline and after each step of IgG-dose-reduction or before if patients experienced worsening of symptoms. We included patients with CIDP from our Neuromuscular clinic.

Results:
65 patients with CIDP had IgG dosage evaluated in this study. Of those n=34 was stable after discontinuation of IgG treatment, n=23 was IgG dependent (n=7 stable at a reduced dose and n=16 stable at starting dose) and for n=8 patients dose reduction was not yet completed.

Conclusions:
We demonstrated that a test battery containing assessments performed by a physiotherapist during tapering down IgG-treatment ensured that relapse was captured early without the risk of chronic adverse effects since all patients that had relapse gained function as pre-relapse-dose.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: CIDP, IgG-dose-reduction, Test battery, Physical function, Physiotherapy

PROMs Assessing HRQOL In Patients With GBS And CIDP: A Systematic Review Of Measurement Properties

Poster No:
P 437

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Introduction:
Guillain-Barre syndrome (GBS) and chronic inflammatory demyelinating polyneuropathy (CIDP) are immune mediated polyradiculoneuropathies, causing progressive weakness and sensory deficits of the limbs. GBS has an acute monophasic course and is usually triggered by a preceding infection. CIDP has a slower progressive and more protracted course than GBS. Both disorders respond to immune-modulatory treatments, but the response varies between patients and many of them report residual deficits, pain and fatigue that may have a considerable impact on their quality of life. Several patient-reported outcome measures (PROMs) have been developed to assess multiple constructs. With this systematic review we aim to provide recommendations on the use of PROMs for measuring health-related quality of life (HQROL) in patients with GBS and CIDP, based on their methodological quality.

Methods:
A systematic literature search for the development and validation of PROMs measuring HRQOL in EMBASE, MEDLINE Web of Science and Google Scholar was conducted. Content of all PROMs that have been developed or validated for patients with polyneuropathy were systematically described and classified based on the Wilson and Clearly model. Measurement properties of PROMs assessing HRQOL in patients with GBS and CIDP were evaluated in accordance with the COnsensus-based Standards for the selection of health Measurement INstruments (COSMIN) guideline for systematic reviews of PROMs.

Results:
The initial search yielded 4,334 articles. In total 68 relevant articles were identified that developed or validated PROMs that measure (aspects of) HRQOL in patients with polyneuropathies. Of all identified PROMs only 5 were developed specifically for GBS and/or CIDP.

Conclusions:
The classification of PROMs for patients with polyneuropathy and the methodological quality assessment of the measurement properties of included PROMs for patients with GBS and CIDP are ongoing and these results will be presented at the upcoming PNS meeting.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Patient-reported outcome measure

Patient-reported Impact Of Guillain-Barré Syndrome (GBS) Based On The Inflammatory Rasch-built Overall Disability Scale (I-RODS)

Poster No:
P 438

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Introduction:
Previous studies have indicated the major and long-term impact of the Guillain-Barré syndrome (GBS) on patients, even after good clinical recovery. The Inflammatory Rasch-built Overall Disability Scale (I-RODS) is a patient-reported outcome measure that measures limitations in daily activities and social participation in patients with immune-mediated neuropathies. The I-RODS is often used in clinical trials to evaluate treatment response, but it was developed in a selected cohort of Dutch patients with various types of immune-mediated neuropathies, which may limit the applicability to GBS and other patient populations, especially those of other cultures. The present study aimed to describe the impact of GBS on daily activities and participation using the I-RODS. In addition, we aim to further validate the I-RODS in GBS since not all measurement properties have yet been assessed.

Methods:
Data from the prospective International GBS Outcome Study (IGOS) and IGOS Zika were used. The I-RODS consists of 24 items, with scores ranging from 0 to 48. Higher scores reflect better patient-reported health. Median I-RODS scores (IQR) were calculated at 26 weeks follow-up. Structural validity, internal consistency, construct validity, and cross-cultural validity were assessed.

Results:
Median I-RODS scores (IQR) were lowest in patients from Bangladesh (38 [27-42]). Higher I-RODS scores were reported by patients from Europe (44 [3-47]), North-America (44 [37-47]), Asia (46 [42-48]) and South-Africa/Argentina/Australia/Brazil (48 [43-48]). Regarding clinical variants, median I-RODS scores (IQR) were the lowest in patients with pure motor GBS (39 [25-44]). Higher scores were reported by patients with sensorimotor (44 [38-48]), Miller Fisher(-overlap) syndrome (46 [42-48]) and other variants including pharyngeal-cervical-brachial weakness, pure sensory and the ataxic form (45 [37-48]). The distribution of I-RODS scores varies across regions ($p < .001$) and in variants ($p < .001$).

Conclusions:
Further Rasch based validation analyses are ongoing and these results will be presented at the upcoming PNS meeting.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Inflammatory Rasch-built Overall Disability Scale

Revisiting The Spectrum Of Neuropathies In A Large Cohort Of IgA Monoclonal Gammopathies

Poster No:
P 439

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Introduction:
The presence of gammopathy in a patient with neuropathy is a diagnostic challenge. Although this has been widely studied with monoclonal IgM, it remains poorly understood for IgA. Nonetheless, monoclonal IgA can induce severe neuropathies, such as AL amyloidosis or POEMS syndrome. Our objective was to study the spectrum of neuropathies within a large cohort of monoclonal IgA.

Methods:
We retrospectively analyzed the neurological and hematological features of all patients newly diagnosed with monoclonal IgA in our center between 2016 and 2020. We determined the prevalence of neuropathies in this population using keywords. Two neurologists independently reviewed all data from the patients with neuropathy and classified them into three groups: 1) IgA-related neuropathies, 2) IgA-unrelated neuropathies with an identified alternative etiology, and 3) neuropathies of uncertain relationship with IgA (NURIA) when the work-up did not show an alternative etiology.

Results:
Among 585 patients with monoclonal IgA, 79 had neuropathy (14%). Among them, ten (13%) presented IgA-related neuropathies: eight AL amyloidosis and two POEMS syndromes, i.e., less than 2% of the whole cohort of monoclonal IgA. Most neuropathies were IgA-unrelated (N=64, 81%), encompassing mainly chemotherapy-induced neuropathies (N=34), diabetes (N=15), alcoholic (N=6), hereditary (N=3), and vasculitis (N=3). Five (6%) patients had NURIA: four presented as chronic idiopathic axonal neuropathy and one as chronic inflammatory demyelinating polyneuropathy. Six patients with both IgG and IgA gammopathy were classified as IgA-related AL amyloidosis (N=1), IgA-unrelated etiologies (N=4), or NURIA (N=1).

Conclusions:
This study described the spectrum of neuropathies associated with monoclonal IgA, exhaustively detected across a five-year period. Neuropathies are rarely IgA-related, and alternative etiologies are much more frequent. Future studies are needed to identify red flags of IgA-related neuropathies since disease-modifying treatments are available. The clinical pattern of NURIA should also be unraveled.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Monoclonal Gammopathy IgA, Peripheral Neuropathy, Paraproteinemia, POEMS syndrome, AL amyloidosis

Small fiber involvement, neuropathic pain and macrophage-dependent axonal pathology in the rat model of experimental autoimmune neuritis

Poster No:
P 440

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Introduction:
Experimental autoimmune neuritis (EAN) is a common animal model for acute human immune-mediated polyneuropathies. Although already established in 1955 and widely studied, most pathophysiological mechanisms still remain unknown.

Methods:
Here, we extensively characterize EAN progression in Lewis rats, including new insights into the integrity of small nerve fibers, neuropathic pain, and macrophage activation. Acute EAN was induced with P253-78 peptide and consequently investigated using the CatWalk XT, electrophysiological and histopathological analyses, qPCR, dorsal root ganglia outgrowth studies, as well as the von Frey hair and Hargreaves test.

Results:
For the longitudinal setup, rats were sacrificed at d10 (onset), d15 (peak), d26 (recovery), and d29 (late recovery). We confirmed the classical T-cell and macrophage-driven inflammation and the primarily demyelinating nature of the EAN. The dual role of macrophages in EAN is implicated by the high number of remaining macrophages throughout the disease progression. Furthermore, different subpopulations of macrophages based on Cx3cr1, Pf4, and Mgl1 expression were identified. In addition, modulation of the sensory system in EAN was detected. An outgrowth of small fibers in the plantar skin at the onset and peak of the EAN parallel to the development of acute hyperalgesia mediated through transient receptor potential vanilloid 1 modulation was evident.

Conclusions:
Our data depict the EAN as a primary demyelinating disease with implicated axonal damage, minor fiber impairment throughout the disease progression course, and the pivotal role of macrophages in the effector and the recovery stage.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Experimental autoimmune neuritis, small fiber, autoimmune neuropathies

Serum Neurofilament Light Chain As a Biomarker For Symptom Fluctuation In Chronic Inflammatory Demyelinating Polyneuropathy Treated With IVIGs

Poster No:
P 441

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Introduction:
Serum neurofilament light chain (sNfl) is a marker for axonal degeneration and is associated with current and future disease activity in neurological disorders. Patient with chronic inflammatory demyelinating polyneuropathy (CIDP) often report a fluctuation of symptoms throughout one treatment cycle with intravenous immunoglobulins (IVIG). The aim of this study was to determine whether sNfl is a suitable biomarker for quantification of patient reported symptom fluctuation.

Methods:
29 patients with the diagnosis of CIDP or a CIDP-variant und current treatment with intravenous immunoglobulin were recruited in this prospective, explorative cohort study and underwent examination before IVIG infusion (T0), in the middle of the treatment interval (T1) and before their next IVIG infusion (T2). Patients were surveyed regarding symptom fluctuation at the last visit. Two groups (Fluctuation of symptoms yes/no) were formed from this survey. At the first visit sociodemographic as well as disease specific data (initial diagnosis, therapy etc.) was collected. sNfl values were compared between the different time points. Grip strength, INCAT ODSS, INCAT ISS, I-RODS, INQoL and PDQ were assessed at every examination. sNfl values were converted into Z-Scores – adapted for age and BMI – for statistical analysis.

Results:
Patients with CIDP show elevated sNfl Z-Scores (Median at baseline: 2.14, IQR: 0.99). There was no significant change of Z-Scores, questionnaire scores or grip strength within the treatment cycle in either group. A change in reported symptom severity did not correlate with a change in sNfl-levels.

Conclusions:
CIDP patients show elevated sNfl-levels. Nevertheless, sNfl is not suitable to reflect patient reported fluctuation of symptoms. Furthermore, repeated sNfl measurements within a treatment cycle with IVIGs seem to have no benefit regarding symptom-monitoring. This indicates that symptom fluctuation under the treatment with IVIGs in patients with CIDP is not caused by a neuroaxonal injury.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: CIDP, sNfL, Biomarker, Clinical Study

Role Of High Resolution Sonography In The Diagnosis Of Inherited And Immune-mediated Neuropathies

Poster No:
P 442

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Introduction:
The aims of this study were to [1] compare the sonographic pattern of peripheral nerve enlargement and vascularity between subjects with inherited neuropathy [Charcot-Marie-Tooth (CMT) disease, hereditary neuropathy with liability to pressure palsy (HNPP)] and subjects with immune-mediated neuropathy [chronic inflammatory demyelinating polyneuropathy (CIDP), CIDP variant, multifocal motor neuropathy (MMN)] [2] study ultrasonographic patterns of nerve enlargement and vascularity that may aid in diagnosis of suspected inherited neuropathy and suspected immune-mediated neuropathy.

Methods:
Patients who met the inclusion criteria of [1] age $\geq$ 21 years and $\leq$ 70 years [2] either an inherited neuropathy [demyelinating CMT disease, axonal CMT disease, HNPP] or an immune-mediated neuropathy [CIDP, CIDP variant, MMN] or suspected inherited neuropathy or suspected immune-mediated neuropathy participated in the study. Ultrasound of nerves was performed using broad frequency (5-18 MHz) transducer and Doppler. Cross-sectional area (CSA), echogenicity and vascularity were assessed at pre-determined sites of median nerve (wrist crease, mid-forearm, mid-arm), ulnar nerve (wrist crease, mid-forearm, 5 cm distal to elbow, elbow groove, 5 cm proximal to elbow), radial nerve (spiral groove), sciatic nerve (thigh), tibial nerve (popliteal fossa, ankle), peroneal nerve (popliteal fossa, fibular head) and sural nerve (ankle).

Results:
Between July 2021 and December 2022, a total of 44 subjects had ultrasound of peripheral nerves. Subjects with demyelinating CMT disease show diffuse enlargement of nerves with higher CSA values. Subjects with CIDP show either normal nerve size or nerve enlargement in a focal or regional pattern with lower CSA values compared to demyelinating CMT disease.

Conclusions:
This pilot study using the cost-effective modality of ultrasound suggests a trend of its utility in deciphering the etiological diagnosis of neuropathy of unclear cause [inherited versus immune-mediated]. The detailed analysis is currently ongoing. The results of analysis will be presented at the Peripheral Nerve Society meeting.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: RIE 2020 NNI Centre Grant - Pilot Study Grant

Keywords: Nerve Ultrasound , Sonography of peripheral nerves , Cross-sectional area (CSA) of nerves , CIDP, CMT

Clinical and neurophysiological aspects of patients with peripheral nervous system disorders related to COVID-19.

Poster No:
P 443

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Introduction:
Since the beginning of the pandemic by SARS-COV-2, in 2019, a great viral neuroinvasive capacity was observed. Later discovered by the affinity foi the angiotensin-converting enzyme receptor 2, expressed on neurons and endothelial cells, as well as multiple pathological mechanisms (inflammatory disease, compression of nerve trunks, neurotoxic drugs, immune dysregulation and others) leading to the involvement of both the central nervous system and the peripheral nerves, in the most varied clinical presentations. Given this prevalence and importance, further investigation and understanding is needed for better treatment and rehabilitation of these patients.

Methods:
We describe a series of 14 cases attended at the outpatient clinic of a university center in Rio de Janeiro - Brazil. The selected patients manifested a new disease affecting the peripheral nerves shortly after COVID infection.

Results:
The selected patients underwent a neurological clinical evaluation, as well as an electroneurophysiological study to confirm the pathology, in addition to complementary work-up (CSF evaluation, laboratory tests and neuroimaging) depending on the case, to exclude differential diagnoses and greater diagnostic accuracy. A direct relationship between the COVID19 infection and the manifestation of several neuromuscular pathologies was evidenced, both with demyelinating or axonal damage, from mild mononeuropathies to severe polyradiculoneuropathies. Among them, we observed: critical illness neuromyopathy, radiculopathies, radiculoplexitis, multiplex mononeuropathies, small fiber neuropathy and polyrradiculoneuropathies (Guillain-Barré Syndrome), as well as its variants: Miller-Fisher Syndrome and variant axonal disorders (Acute Motor Axonal Neuropathy) and cranial nerve involvement (Bickerstaff Brainstem Encephalitis).

Conclusions:
The relationship between the covid infection and the emergence of peripheral nerve diseases has been consolidating, potentially treatable if promptly identified, resulting in a better clinical outcome for the patient and a lower burden on the health system.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: COVID, Peripheral neuropathy, Peripheral nervous system

A Rare Case Of Angioimmunoblastic T Cell Lymphoma Presenting With Paraneoplastic Vasculitic Peripheral Neuropathy

Poster No:
P 444

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Introduction:
Angioimmunoblastic T cell lymphoma (AITL) is a rare form of non-Hodgkin lymphoma (NHL) with an incidence of 0.05 cases per 100,000 person years. It usually presents with B symptoms, anemia, skin rash, lymphadenopathy, and hepatosplenomegaly. Paraneoplastic vasculitis and peripheral neuropathy are less commonly reported occurrences. Presence of anti-phospholipid (aPL) antibodies with or without clinical evidence of thrombosis is even rarely reported in association with lymphoma.

Methods:
This abstract is based on a case report

Results:
A 59-year-old male presented with a two-month history of gradually worsening bilateral asymmetrical upper limb and lower limb numbness and a later development of weakness. One month later he had painful swellings of digits with cyanosis, which later evolved into digital dry gangrenes. Examination revealed generalized lymphadenopathy without hepatosplenomegaly, bilateral asymmetrical sensory impairment, and lower limb weakness. Lymph node biopsy revealed the diagnosis of AITL. Nerve conduction studies (NCS) demonstrated mixed sensory motor axonal polyneuropathy. Sural nerve biopsy showed evidence of leukocytoclastic vasculitis. In addition, he had positive lupus anticoagulant and anti-cardiolipin IgM antibodies without any clinical evidence of thrombosis. Bone marrow infiltration was also present at the time of diagnosis, and he succumbed to death after one month of initial presentation.

Conclusions:
NHL, especially peripheral T cell lymphoma (PTCL) can present with cutaneous manifestations and digital gangrenes mimicking autoimmune rheumatologic diseases. The presence of immune markers like rheumatoid factor, antinuclear antibodies, aPL antibodies further mask the underlying lymphoma. Peripheral neuropathy can be a great diagnostic value in this type of presentations because of its atypical nature in early rheumatologic disorders and its diagnostic yield with nerve biopsy. Thus, the knowledge of rare, atypical presentations can prevent undue delays in the diagnosis and the patient will be benefitted with the institution of early treatment.

References:
Yes

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Grant Support:

Keywords: Angioimmunoblastic T cell lymphoma, Paraneoplastic vasculitis, Paraneoplastic vasculitic neuropathy , Antiphospholipid antibodies

Neuropathies Related to Hepatitis E Virus Infection in Switzerland: A Prospective, Matched Case-control Study

Poster No:
P 445

Authors:
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Introduction:
Acute hepatitis E virus (HEV) infection recently emerged as a potential trigger for acute immune neuropathies, but prospective controlled studies to investigate causality are lacking. We compared the frequency of acute HEV infection in patients with Guillain-Barré syndrome (GBS), neuralgic amyotrophy (NA), and facial nerve palsy with a control population.

Methods:
Multicentre (11 Swiss centres), prospective, observational case-control study over 3 years (09.2019-10.2022). All patients were recruited within 3 months from disease onset. Controls were healthy blood donors matched for age, sex, geographical location, and time. Diagnostic criteria for acute hepatitis E were reactive serum anti-HEV IgM and anti-HEV IgG assays (ELISA test) and/or HEV RNA detection in serum by Real-time PCR. RT-PCR on sera (HEV RNA detection) was performed to confirm IgM+ results.

Results:
We included 180 patients (59 GBS, 51 NA, and 70 facial palsy) and corresponding controls (for both groups: median age 51 years; male 48%). Six IgM+ cases were detected in the NA group, two in the GBS group, and none in the facial palsy group. No IgM+ was detected in the controls. Cases with acute HEV infection had significantly higher values of ALT and GGT at disease onset. The Fisher's exact test showed a moderate association ($p=0.027$; Cramér's $V = -0.25$) only between acute HEV infection and NA.

Conclusions:
Our study suggests a causal association between acute HEV infection and NA (10% of cases), but not with other autoimmune neuropathies such as GBS nor with facial nerve palsy.

References:

No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Neuropathies , Hepatitis E virus

Immune Events Preceding Neuralgic Amyotrophy

Poster No:
P 446

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Introduction:
Infections and vaccinations have been identified as potential triggers preceding neuralgic amyotrophy (NA), but the exact type and frequency of the different agents in Europe is largely unknown.

Methods:
Swiss multicentre prospective study over a 3-year period (09.2019-09.2022). NA was diagnosed by neuromuscular experts according to existing criteria and electrodiagnostic studies. Clinical data and biological samples of NA patients were collected in the acute phase of the disease (within 90 days from onset). Serological tests were all performed in one reference microbiology laboratory.

Results:
Disease onset was preceded by an identifiable immune trigger in 23/42 patients (54.8%). Infection in 16/42 (38%) and COVID vaccination in 7/42 (16.7%). Viral infections were the most common (n=13, 31%). Identified (mostly by RT-PCR methods) viral agents were hepatitis E virus (HEV, n=6), Epstein-Barr virus (EBV, n=1), SARS-COV-2 (n=2), influenza (n=2), human immunodeficiency virus (HIV, n=1) and Parvovirus B19 (n=1). A bilateral involvement of NA was found in 7/42 (16.7%) patients and was always associated with a preceding systemic viral infection.

Conclusions:
Our data support a para-infectious pathogenesis of NA in the majority of cases. A bilateral involvement in NA could serve as a clinical marker for preceding viral infection.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Neuralgic amyotrophy, Infection, Vaccination

Precise nerve matching approach in human peripheral nerve graft transplantation

Poster No:
P 447

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Introduction:
Nerve morphology and its role in regeneration process following peripheral nerve injury and repair has been an active area of research for many years. A more comprehensive understanding of nerve morphology and its effects on nerve transplants can improve clinical outcomes. This research categorized obturator, median and femoral nerve morphology based on sex, laterality, length, diameter, and number of fascicles, looking for trends in nerve organization that could improve nerve regeneration after transplantation.

Methods:
Obturator, median and femoral nerves were isolated from 25 human donors' postmortem. Cross-section samples were collected from both the left and right nerves.

Results:
The tissue samples were visualized, photographed and analyzed. Preliminary results indicated that both male and female obturator and femoral nerves had more fascicles on the left side than the right side. Obturator nerve length was similar in both sides (left=10.83cm; right=10.86cm). The obturator nerve diameter was, on average, 2.67mm in males and 1.91mm in females. Diameter of the femoral nerve was bigger in males (male=5.09mm, female=4.17mm). Median nerves presented similar diameter and fascicles number in males (diameter= 2.53mm, fascicles number= 14.61) and females (diameter=2.43mm, average of fascicles number=14.63). Furthermore, both obturator and femoral nerves revealed differences in percentage of intra nerve connective tissue; overall, females presented more non-nerve tissue than males.

Conclusions:
The findings of this research will lead to development of a rational and precise nerve matching approach in graft transplantation. We identified specific trends and landmarks in the obturator, median and femoral nerves, and we believe that these findings will help to best match donor to recipient, optimize surgical procedures, and improve patients' functional outcomes after transplantation. This research is generating a data bank that will include morphometrics and landmarks. This data bank will be available to the medical community and tissue bank companies, as a template to facilitate peripheral nerve allograft matching.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: transplantation, morphometrics, nerve morphology, human study, peripheral nerve injury

Production Of Paranodal Autoantibodies By PBMCs In Vitro

Poster No:
P 448

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Introduction:
Most patients with paranodal autoantibodies do not respond to standard therapy with immunoglobulins, but well to B-cell depleting treatment with rituximab. Some patients show persistent high serum autoantibody titers after therapy with rituximab. To investigate the production of paranodal autoantibodies in vitro at onset, under treatment and after remission of disease, we compared the autoantibody production by peripheral blood mononuclear cells (PBMCs) in vitro with the serum titer.

Methods:
PBMCs from five patients with Contactin-1 (CNTN1) autoantibodies, two patients with Neurofascin-155 (NF155) autoantibodies and two Pan-Neurofascin (PanNF) patients were stimulated with interleukin-2 and resiquimod for 10 days. Antibodies against NF155, CNTN1, tetanus and total IgG were measured in the supernatant using enzyme-linked immunosorbent assay.

Results:
Autoantibody production by PBMCs in vitro was associated with high serum titers and was detected in two CNTN1-, one NF155- and one PanNF-positive patient. The two CNTN1-positive patients were additionally tested after treatment with rituximab. One patient became seronegative and no autoantibody production by PBMCs could be induced anymore. In the other patient, anti-CNTN1 autoantibodies were still detectable after treatment in the serum and in the supernatant of stimulated PBMCs. No autoantibody production by PBMCs in vitro could be induced in three patients formerly seropositive for anti-CNTN1 or anti-NF155 who were seronegative and in remission at the day of inclusion and in two patients with a low serum titer.

Conclusions:
Our data demonstrate an association between the serum autoantibody titer and the autoantibody production by PBMCs in vitro. This observation and the production of autoantibodies by PBMCs in vitro in one patient with a high serum autoantibody titer under treatment with rituximab points towards a persistent autoantibody production in the peripheral blood because of an insufficient B-cell depletion and argues against autoantibody production by long-lived plasma cells in the bone marrow as the major reason for persistent seropositivity.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: paranodal autoantibodies, PBMC, autoimmune nodopathy, rituximab

Autonomic nervous system involvement in chronic inflammatory demyelinating polyradiculoneuropathy: a systematic review.

Poster No:
P 449

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Introduction:
Although dysautonomia is a well-recognized complication of acute demyelinating polyradiculoneuropathy, it is rarely reported and evaluated in chronic demyelinating neuropathies. The purpose of this systematic review is to search and synthesize the current literature on the prevalence and type of autonomic dysfunction (AD) in chronic inflammatory demyelinating polyradiculoneuropathy (CIDP).

Methods:
PubMed and Web of Science were searched for studies reporting AD in CIDP.

Results:
Thirteen studies, including 366 patients with CIDP, were found eligible for the review. Eight studies used autonomic tests only as an additional component of the comprehensive clinical evaluation, and found that dysautonomia in CIDP may indicate the presence of a comorbid disease (e.g., diabetes) and facilitate the differentiation of CIDP from other neuropathies (e.g., amyloid neuropathy). Five studies performed quantitative assessment of autonomic function in CIDP as a primary goal. Three studies have used the Composite Autonomic Severity Score (CASS) to assess severity and distribution of dysautonomia. The reported prevalence of dysautonomia in CIDP during quantitative assessment of autonomic function ranged from 25% to 89%, depending on the battery of tests used, with CASS not exceeding 4 points. The abnormalities in autonomic tests indicated both sympathetic and parasympathetic dysfunction and did not correlate with the duration, severity and variant of CIDP.

Conclusions:
Clinical or subclinical involvement of the ANS has been shown to be common and relatively mild in CIDP. Future prospective, multicenter and unbiased studies are needed to evaluate the frequency, characteristics, impact on disability, and response to treatment of dysautonomia in CIDP.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: Not applicable

Keywords: chronic inflammatory demyelinating polyradiculoneuropathy , autonomic dysfunction, autonomic nervous system, autonomic function tests

The occurrence of dysautonomia and fatigue in chronic inflammatory demyelinating polyradiculoneuropathy.

Poster No:
P 450

Authors:
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Introduction:
Fatigue and autonomic dysfunction remain underestimated clinical features significantly affecting the daily functioning of patients with chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). We aimed to evaluate the occurrence and severity of patient-reported autonomic symptoms and fatigue in CIDP patients.

Methods:
Thirty-four clinically stable CIDP patients with a mean age of 59.9 ±12.9 years (73% male) receiving intravenous immunoglobulin underwent quantitative assessment of autonomic function using Composite Autonomic Symptom Score (COMPASS-31) and fatigue severity by the use of Fatigue Severity Scale (FSS).

Results:
The mean COMPASS-31 total score was 14.1 ±11.0. Gastrointestinal symptoms (score > 0) were reported by 29 (85.3%) patients (mean score 4.9 ±4.0), pupillomotor by 23 (67.6%) patients (mean score 1.3 ±1.1), secretomotor by 18 (52.9%) patients (mean score 2.8 ±1.4), bladder by 14 (41.6%) patients (mean score 0.8 ±1.1), orthostatic by 12 (35.2%) patients (mean score 3.6±5.4), and vasomotor by 6 (17.6%) patients (mean score 0.8±1.6). All patients were fatigued (mean FSS score 51.6 ±10.6). There were no associations between COMPASS-31 total score and its subscores with fatigue severity.

Conclusions:
Patient-reported autonomic signs and fatigue are common and independently occurring non-motor symptoms of CIDP. Future prospective, multicenter and unbiased studies are needed to evaluate the frequency and characteristics of dysautonomia and fatigue severity in CIDP patients.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: chronic inflammatory demyelinating polyradiculoneuropathy , autonomic dysfunction, fatigue

A case of combined central and peripheral demyelination vs adult onset leukodystrophy; A diagnostic dilemma

Poster No:
P 451

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Introduction:
We report a 66-year-old man who presented with a 10-year history of episodic bilateral symmetrical upper limb and lower limb numbness and weakness associated with a disabling upper limb tremor responsive to steroid therapy. Later he presented with an episode of optic neuritis leading to brain imaging showing confluent white matter hyperintensities which lead to a diagnostic dilemma.

Methods:
Examination revealed lower motor neuron signs on upper limbs with significant wasting with areflexia and an action postural 5Hz tremor whilst lower limbs demonstrated hyperreflexic knee jerks with absent ankle reflexes. Sensory examination revealed a glove and stocking sensory loss with loss of proprioception. Nerve trunk thickening was observed at greater auricular nerves and ulnar nerves. MMSE was 30/30.

Results:
Nerve conduction demonstrated possible demyelinating polyneuropathy according to 2021 EAN/PNS criteria. Cerebrospinal fluid was acellular with high protein level of 135mg/dl. Nerve biopsy confirmed onion bulb appearance on teased fibers favoring chronic inflammatory demyelinating polyneuropathy. Spinal imaging demonstrated a short segment T2 hyperintensity with contrast enhancement involving lateral corticospinal tract area in cervical spine suggestive of demyelination explaining the spasticity. MRI brain showed asymmetrical confluent areas of T2 hyperintensities perpendicular to corpus-callosum involving subcortical u-fibers and blackholes suggestive of demyelination. CSF for oligoclonal bands was negative. VEP was delayed bilaterally. NMO antibody screening was negative. Screening for secondary causes including sarcoidosis, retroviral disease, syphilis, leprosy, vasculitis and paraproteinaemia was unremarkable. Serum cortisol, urine sulfatide levels were normal. CSF and serum lactate levels were normal. His serum anti-Neurofascin-155 antibody level was sent to Mayo clinic,US.

Conclusions:
He had suboptimal response to IV methylprednisolone therapy and immunoglobulin therapy. Later plasma exchange 5-cycles were carried out showing an excellent response particularly with the tremor. Maintenance therapy is with azathioprine and oral steroids. The presence of confluent brain lesions there was a delay in commencing immunotherapy highlighting the importance of recognizing this entity.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Combined central peripheral demyelination, CCPD, Leukodystrophy

External Validation of Prognostic Model For Time To Achieve Independent Walking In Guillain-Barré Syndrome Children

Poster No:
P 452

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Introduction:
Guillain-Barré Syndrome (GBS) is an immune-mediated peripheral neuropathy. Clinical features and outcomes in children differ from adults. The first prognostic model to predict outcomes in children recently developed by our group. This model is based on GBS disability score at point of maximum weakness and nerve conduction study (NCS) result. The model can predict time to achieve independent walking in individual pediatric patients with GBS and assist clinicians to optimize treatment and guide decisions on rehabilitation to prevent long-term disability. Further studies of predictive factors and external validation to improve precision of the model is needed. Objectives is to demonstrated study protocol to validate the prognostic model for time to independent walking in children with GBS. To find a collaboration from GBS working groups or consortium worldwide in order to get international, large sample size of GBS in children.

Methods:
Factors associated with independent walking were analyzed with the Kaplan-Meier method. A prediction model was developed based on regression coefficients from Cox's proportional hazard model.

Results:
The disability score at maximum weakness and NCS results were associated with independent walking. The equation of predictive score is 1 x (disability score) + 4 x (NCS). Scores range from 0 to 5. A higher score correlated with better prognosis. A score of 5 predicts 34 days to achieve independent walking while a score of 0 predicts 5 months (mean 158 days, $p = 0.008$). Kaplan–Meier curve of probability to achieve independently walking in each score group will be showed.

Conclusions:
This scoring system for pediatric patients provides predicts the time needed to achieve independent walking, an important milestone of recovery for communication with parents, and to assist clinicians to optimize treatment. Further studies of predictive factors and external validation with a large, international sample size are needed to improve precision of the model.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: none

Keywords: GBS, outcome , score, predict , disability

Multiple mononeuropathies in AL Amyloidosis

Poster No:
P 453

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Introduction:
Focal amyloidosis is a rare condition characterized by the accumulation of amyloid protein deposits in specific organs, including the peripheral nervous system.

Methods:
In this retrospective study, we identified 80 patients who had a diagnostic code designated as amyloidosis at our tertiary care center between January 1, 2007 and December 31, 2020.

Results:
We identified 11 cases, including AL Lambda(n=6), and Kappa (n=5). Mean age of onset 61 years, majority of patients were males (63%). Median time from onset to diagnosis was 63 months (range: 25 to 149). Follow up time was 124 months (range: 91 to 293). Most common presenting symptoms were weakness and sensory deficits. Pain was part of the presenting symptoms in 82% of patients. Median NIS scores at presentation was 35 (range: 11 to 67). Electrodiagnostic testing was abnormal in all patients, with findings consistent with focal areas of axonal degeneration in individual nerves, plexi and roots. MRI imaging showed nerve enhancement or enlargement in 62.5% of cases. Nerve biopsy findings included interstitial amyloid deposits and perivascular inflammatory collections. Outcome data available in 10 patients with only 64%% (n=7) were treated. Three patients died during follow-up. Treatments included cyberknife in one patient, remaining 5 patients received combination of chemotherapy (rituximab=2, bendamustin=1 and melphalan=1) and stem cell transplantation (n=3). None of the patients achieved INCAT Disability Scale score reduction of ≥ 1 or a ≥ 8-point reduction in NIS score. Five patients worsened while on treatment and the other 5 patients were stable at last follow-up.

Conclusions:
Our investigation underscores the necessity of including focal amyloidosis in the differential diagnosis of multifocal sensory and motor neuropathies, particularly in elderly male subjects. While the progression of symptoms is a frequent occurrence, mortality appears to be unaffected by this condition.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Amyloidosis, Multiple mono neuropathy

Clinical features of autoimmune nodopathy with anti-neurofascin 155 antibody in Koreans

Poster No:
P 454

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Introduction:
Autoimmune nodopathy has emerged as a new category of acquired demyelinating neuropathies recently and refers to an immune-mediated neuropathy associated with autoantibodies against proteins at the node and paranode of Ranvier. Anti-neurofascin 155 antibody is one of the most common antibodies associated with autoimmune nodopathy. However, autoimmune nodopathy with anti-neurofascin 155 antibody has not been reported in Korea yet. We aimed to investigate the clinical features of Korean patients with anti-neurofascin 155 antibody positive autoimmune nodopathy.

Methods:
Sera from 68 patients fulfilling diagnostic criteria of chronic inflammatory demyelinating polyneuropathy (CIDP) were screened for anti-neurofascin 155 using cell-based assay (CBA) and enzyme-linked immunosorbent assay (ELISA). The anti-neurofascin 155 positive sera were additionally tested for neurofascin 155 immunoglobuin G (IgG) subclasses and for anti-neurofascin 186 and anti-neurofascin 140 antibodies. Clinical features and response to therapy were reviewed retrospectively.

Results:
Among the 68 patients, six (8.8%) patients were positive for anti-neurofascin 155 antibody in both CBA and ELISA. Of the six patients who were positive for anti-neurofascin 155 antibody, one patient was positive for anti-neurofascin 186 and anti-neurofascin 140 antibodies. IgG4 was predominant in four patients. Mean age at onset was 32.2 years. All six patients presented with progressive sensory ataxia. Three patients had tremor and two patients had facial palsy. Among the five patients treated with corticosteroids, two patients showed partial response and the other three patients showed no response. All six patients were treated with IV immunoglobulin (IVIg). Five patients showed partial or poor response and one patient had a good response to IVIg. Three patients were treated with rituximab and all three showed good response.

Conclusions:
Anti-neurofascin 155 antibody was found in approximately 9% of Korean patients fulfilling CIDP diagnostic criteria. Clinical characteristics and treatment response were consistent with those in previous reports.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korean government (MSIT) (No. NRF-2020R1C1C1010130).

Keywords: Autoimmune nodopathy, Anti-neurofascin 155 antibody

Tolerance and Safety of Subcutaneous Immunoglobulin via Pre-filled Syringes for Inflammatory Neuropathy: A Retrospective Cohort Study

Poster No:
P 455

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Introduction:
Subcutaneous Immunoglobulin (SCIg) is safe and effective for the treatment of both Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) and Multifocal Motor Neuropathy (MMN). Mode of delivery is normally via a syringe pump due to large infusion volumes. Pre-filled syringes (PFS) of Immunoglobulin are available for SC delivery given by manual push (PFS-Manual Push). It is often avoided in inflammatory neuropathy due to large doses. However, within our cohort, many patients have switched to PFS-Manual Push. The aim was to assess tolerance and safety of PFS-Manual Push in a single centre, inflammatory neuropathy cohort via a retrospective case note review.

Methods:
All Inflammatory Neuropathy patients on Immunoglobulins in a single neuroscience centre in the north west of England between January 2020 to November 2022 were identified via the National Immunoglobulin Database. Data of diagnosis, duration and type of treatment, reason for changing to SC PFS-Manual Push, dose, adverse events, and attrition were collected.

Results:
81 patients with inflammatory neuropathy treated with SCIg were identified. 35 (43%) used PFS-Manual Push. 17 of these converted directly to PFS-Manual push from IVIg, whereas 8 initially used a pump. 10 were naïve to immunoglobulin. The majority of patients switched to PFS due to supply reasons. The mean dose of SCIg weekly given via PFS-Manual Push was 20g (range 12-30g), but most patients split into two sessions, mean 12g (8g -16g) per session. 4/35 patients reported adverse events. These were localised pain and swelling with 1 patient stopping SCIg via PFS-Manual Push. 3 patients managed adverse events by slowing the rate of administration.

Conclusions:
Despite high SCIg doses in Inflammatory Neuropathy, PFS delivered via Manual Push was a safe and tolerated route of administration in a single centre cohort.

References:
Yes

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References 2:

Harbo, T., Andersen, H., Hess, A., Hansen, K., Sindrup, S. H., & Jakobsen, J. (2009). Subcutaneous versus intravenous immunoglobulin in multifocal motor neuropathy: a randomized, single-blinded cross-over trial. European journal of neurology, 16(5), 631-6

References 3:

References 4:

Grant Support:

Keywords: subcutaneous immunoglobulin, CIDP, inflammatory neuropathy, immunoglobulin, MMN

Severe Lower Back Pain Improved with Corticosteroid in Two Cases of Acute Motor Axonal Neuropathy

Poster No:
P 456

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Introduction:
Back pain has been reported in some cases, however severe back pain with radiating pain has not been recognized as a main feature of acute motor axonal neuropathy (AMAN). We report 2 cases of AMAN with severe back pain with radiating pain which were improved with corticosteroid.

Methods:
....

Results:
Case 1: A 48-year-old man presented with swallowing difficulty and limb weakness. On admission, the motor power was MRC 3 to 4 grade in both extremities. There were no sensory symptoms. Nerve conduction studies (NCS) revealed axonal motor neuropathy. We diagnosed him as having AMAN, and started 0.4 mg/kg/day of intravenous immunoglobulin (IVIg) for 5 days. After the admission, he complained severe back pain with radiating pain in both leg and shoulder which was not improved with acetaminophen, tramadol, and gabapentin. We treated him with 3 days of methylprednisolone (1 g/day). The day after injection of the steroid, the pain was immediately improved. Case 2: A 59-year-old women visited because of limb weakness and both hand numbness. Motor grade was MRC 3 to 4 in all extremities. Decreased amplitudes with mild latency delay were observed in motor NCS. Under the diagnosis of AMAN, she was treated with IVIg for 5 days. On the day after admission, she complained severe back pain with left thigh and neck pain. She took acetaminophen and tramadol, but the pain was not improved at all. She felt pain improvement rapidly with dexamethasone (20 mg/day) for 3 days.

Conclusions:
The mechanism of severe back pain in GBS has not been established. The postulated mechanism is inflammation of the nerve roots or denervated muscles. Corticosteroid was effective in controlling the pain in these cases by reducing inflammation of nerve or muscles. Further study regarding back pain and it's management in GBS is needed.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Guillain barre syndrome, neuropathic pain, corticosteroid

Sural nerve biopsy utility assessment by histologic preparations: An observational cohort of 100 consecutive cases

Poster No:
P 457

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Institutions:
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Introduction:
Nerve biopsies are reported to assist in neuropathy diagnosis. Systematic study of their value to inform and alter treatment recommendations and the quantitated value of the separate histologic preparations utilized is lacking and needed for evidence-based practice.

Methods:
Consecutive sural nerve biopsies (50 internal and 50 external referrals) were reviewed. Standard histological preparations plus graded teased nerve fibres (GTNF), immunohistochemistry, and epoxy-semithin morphometric analysis were studied. Nerve fiber and interstitial abnormalities were scored for each preparation by three examiners masked to case identification. Multivariate modeling was used to inform on the best combination of tests vs a gold standard of the full biopsy report plus morphometric analysis. Resulting clinicopathological diagnosis and treatment recommendations were reviewed.

Results:
Paraffin-stained sections best recognized interstitial abnormalities: Epineurial inflammation (n=59); vasculitis with vessel wall destruction (n=14); amyloidosis (n=2); and noncaseating granuloma (n=1). Vasculitic neuropathy associated with GTNF axonal degeneration (79%) with OR 3.8, 95%CI [1.001, 14.7], p=0.04, not significantly seen with the other preparations. Teased fiber abnormalities correlated with clinicopathologic diagnosis e.g. chronic inflammatory demyelinating polyradiculoneuropathy, 85% (11/13); amyloid fibrils in amyloidosis, 50% (1/2); polyglucosan fibers in adult-onset polyglucosan disease 100% (1/1). GTNF and paraffin stains significantly correlated with fiber density determined by morphometric analysis (GTNF: OR 9.9, p<0.0001, paraffin: OR 3.8, p=0.03) not significant with semithin epoxy: OR 1.1, p=0.90, or immunohistochemistry: OR 2.4, p=0.18). GTNF combined with paraffin sections had the highest accuracy for predicting clinicopathologic diagnosis and fiber density with 0.86 C-stat prediction versus morphometric analysis. Among internal cases sural biopsy aided clinicopathologic diagnosis: immunotherapy initiation (44%); reduced immunotherapy (18%); and escalated immunotherapy (8%).

Conclusions:
Sural nerve biopsy results have high diagnostic utility frequently altering treatment recommendations in selected patients. Paraffin stains combined with GTNF provide the highest diagnostic neuropathic and interstitial accuracy overall and approximate the fiber density measurements of morphometric analysis by epoxy-semithin sections.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Biopsy, Neuropathy, histopathology, Immunostains, teased fibers

Amyloid-like IgM Deposition Neuropathy with Multiple Mononeuropathies and Generalized Neuropathy

Poster No:
P 458

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Introduction:
Amyloid-like IgM deposition neuropathy is a distinct entity in the setting of IgM monoclonal gammopathy in which endoneurial perivascular entire IgM-particle accumulation leads to a painful sensory followed by motor peripheral neuropathy.

Methods:
We report a 77-year-old man presenting with progressive multiple mononeuropathies starting with painless right foot drop .

Results:
Electrodiagnostic studies showed severe axonal sensory-motor neuropathy superimposed by multiple mononeuropathies. Laboratory investigations were remarkable for biclonal gammopathy of IgM kappa, IgA lambda and severe sudomotor and mild cardiovagal autonomic dysfunction . A right sural nerve biopsy showed multifocal axonal neuropathy, prominent microvasculitis, and prominent large endoneurial deposits of Congo-red negative amorphous material. Laser dissected mass spectrometry-based proteomics identified IgM kappa deposit without serum amyloid-P protein.

Conclusions:
This case has several distinctive features, including motor preceding sensory involvement, prominent IgM-kappa proteinaceous deposits replacing most of the endoneurium, a prominent inflammatory component, and improvement of motor strength after immunotherapy.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: IgM deposition neuropathy, IgM monoclonal gammopathy, microvasculitis, Waldenström's macroglobulinemia, Amyloid-like

Distinctive Clinical Features Separate Nerve Large-Arteriole Vasculitis from Nerve Microvasculitis

Poster No:
P 459

Authors:
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Introduction:
Vasculitic neuropathy is caused by inflammatory destruction of nerve blood vessels resulting in nerve ischemia. Nerve vasculitis can be divided into two categories based on vessels size – large arteriole vasculitis and microvasculitis. Herein, we characterize the clinical features of large arteriole vasculitis compared to microvasculitis.

Methods:
This is a retrospective, observational cohort study of patients evaluated and biopsied at a single center between 2001 to 2020. We collected clinical and histopathological data from patients whose nerve biopsies were either diagnostic or highly suggestive of nerve vasculitis.

Results:
278 cases were identified; 125 cases of large arteriole vasculitis and 153 cases of microvasculitis. Nerve large arteriole vasculitis presented with more acute vs. subacute/ chronic onset (50.4% vs 26.8%) than nerve microvasculitis (33.6% vs 57.5%) ($p= 0.0001$). Nerve microvasculitis had longer time to diagnosis (10.5 vs 4.3 months; $p < 0.0001$), and longer time to plateau (8.9 vs 3.5 months; $p <0.0001$). Nerve large arteriole vasculitis typically presented as asymmetric polyneuropathy (48.0%) whereas nerve microvasculitis typically presented as radiculoplexus neuropathy/ polyradiculoneuropathy (more proximal involvement) (43.8%) ($p < 0.0001$). Systemic autoimmune disease was more common in nerve large arteriole vasculitis (68.0% vs 20.9%, odd ratio, 7.8; 95% confidence interval [CI], 4.5-13.4; $p < 0.0001$). The diagnosis of nerve microvasculitis was significantly related to non-systemic vasculitis (71% vs 21%, odd ratio, 9.1; [95%CI], 5.2-15.9; $p<0.0001$). Nerve microvasculitis had more autonomic involvement (24.2% vs 7.2%, odd ratio, 4.1; [95% CI], 1.9-8.9; $p = 0.0002$).

Conclusions:
Nerve large arteriole vasculitis and nerve microvasculitis have different but overlapping clinical features. Nerve large arteriole vasculitis presents most often with acute onset, distal asymmetric polyneuropathy pattern, and more often has systemic involvement. In contrast, nerve microvasculitis presents most often with subacute/ chronic onset, as a radiculoplexus neuropathy or polyradiculopathy with autonomic involvement and is more often a form of non-systemic vasculitis.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Vasculitic neuropathy, Nerve large-arteriole vasculitis, Nerve microvasculitis, Clinical features, Nerve Biopsy

Treatment of CIDP and MMN: Current Practice Patterns of Neurologists in Germany

Poster No:
P 460

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Introduction:
Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) and Multifocal Motor Neuropathy (MMN) are chronic immune-mediated neuropathies. For CIDP, diagnosis and treatment EAN/PNS Guidelines were updated in 2021 whereas for MMN EFNS/PNS guidelines from 2010 are still used. The aim of this survey was to evaluate clinical practice patterns of German neurologists for CIDP and MMN patients in initial and maintenance treatment with Intravenous Immunoglobulins (IVIg).

Methods:
14 German office-based (36%) and hospital-based (64%) neurologists, up to now, completed a cross-sectional quantitative online survey comprising 16 questions each for CIDP and MMN.

Results:
In line with EAN/PNS guidelines 93% of the neurologists stated using IVIg (57%) or corticosteroids (36%) as initial treatment for CIDP, 7% prefer plasma exchange. In accordance with the guidelines, all neurologists use IVIg as initial treatment for MMN. For both neuropathies, recommended initial doses of 2.0 g/kg body weight were applied by 85% of the neurologists. For maintenance treatment, 1.0 g/kg body weight dosing was mostly agreed (93% of neurologists) for CIDP, in contrast to only 58% of the neurologists for MMN. High variability existed regarding frequency, duration of IVIg therapy before evaluating response, outcome measures, dose adjustment and treatment schemes in case of relapses. Interestingly, about one third of neurologists (36% for CIDP, 29% for MMN) continue IVIg long-term with no attempt to wean patients from IVIg.

Conclusions:
There is considerable variability regarding daily management of IVIg treatment for CIDP and MMN in Germany. To gain further insights on individualization of therapy during long-term treatment in real-world practice an observational study is currently conducted.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: This study is funded by Grifols Deutschland GmbH.

Keywords: Chronic Inflammatory Demyelinating Polyneuropathy, Multifocal Motor Neuropathy , Intravenous Immunoglobulins, IVIg

Lenalidomide in the Treatment of anti-Myelin Associated Glycoprotein Neuropathy – A Phase 1b Nonrandomized Controlled Trial

Poster No:
P 461

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Institutions:
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Introduction:
Anti-MAG Neuropathy is a debilitating demyelinating autoimmune peripheral neuropathy with no approved therapies. Lenalidomide, an immunomodulating therapy used in plasma cell dyscrasias, has not been formally explored.

Methods:
This phase 1b, open-label, single-arm, dose-finding non-randomized controlled trial was conducted from June 2018 through March 2022, during which safety and efficacy outcomes were monitored. The original study design was to have a dose-escalation/dose-extension phase (1-2 years), followed by a dose-expansion (1 year) phase. The main outcome was the maximal tolerated dose (MTD) of lenalidomide, ascertained using a Bayesian Optimal Interval Design. We hypothesized prior to study initiation that the MTD would be 25 mg, given the good tolerability of drug in clinical practice. We also sought to explore therapeutic efficacy.

Results:
Eleven patients enrolled in the study (10 men), with a mean age of 67.6 years and mean disease duration of 8.5 years. The study terminated early due to a higher-than-expected occurrence of non-DLT VTE events (3 total). The dose-expansion phase was not pursued. The calculated MTD from the dose-escalation/extension phase was 25 mg. Nevertheless, a recommended phase 2 dose of 15mg was advised due to the high VTE occurrence. No serologic or clinicometric measures showed statistically significant improvement at month 12 compared with baseline.

Conclusions:
Lenalidomide was associated with higher-than-expected VTE events in anti-MAG neuropathy patients. Although the MTD was 25 mg, we do not recommend this dose due to high VTE risk. Furthermore, antiplatelet therapy appears insufficient as VTE prophylaxis for lenalidomide in anti-MAG neuropathy, despite existing myeloma guidelines. Anticoagulation therapy may be necessary.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: Bristol Myers Squibb. GBS-CIDP Foundation.

Keywords: MAG neuropathy, Lenalidomide, maximum tolerated dose, clinicometric outcomes, venous thromboembolism

Case series of acute peripheral neuropathies associated with COVID- 19 vaccination

Poster No:
P 462

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Introduction:
Vaccination has been critical to managing the COVID-19 pandemic. However, autoimmunity of the nervous system can be triggered or enhanced by the contents of vaccines. Here, we report a case series of acute peripheral neuropathies following vaccination against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

Methods:
We obtained the patients' history, performed clinical neurological examination and electromyoneurography on all subjects. If necessary, magnetic resonance imaging, laboratory testing, including cerebrospinal fluid analysis and specific antibody testing, were performed.

Results:
We report on 11 patients (range: 30-90 years old) who presented at our center between January 2021 and February 2022. Patients presented with peripheral neuropathies of acute onset of 15 minutes to 40 days after vaccination with different types of COVID-19 vaccines: one with phrenic nerve palsy, not previously described, three with unilateral peripheral facial palsy, two with acute inflammatory demyelinating polyneuropathy (including one with additional facial bi-plegia), one with acute axonal sensory polyneuropathy, and four with acute brachial neuropathy. Most cases (9/11) resolved with a rapid, complete or partial recovery.

Conclusions:
Vaccines against SARS-CoV-2 may lead to acute peripheral neuropathies as potential side effects. Albeit our observation shows that during extensive vaccination programs, negative side effects on the peripheral nervous system might occur, most of them had merely a benign clinical presentation and course of reported symptoms, this should not hinder the prescription of vaccines. More extensive studies are needed to elucidate populations at risk of developing peripheral neuropathies and mechanisms of autoimmune response in the nervous system.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Inflammatory neuropathy, Vaccination, Guillain-Barré syndrome, Facial palsy, Acute sensory neuropathy

A patient with hepatitis B virus related Cryoglobulinemic Neuropathy

Poster No:
P 463

Authors:
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Introduction:
To report a case of HBV related Cryoglobulinemic Neuropathy

Methods:
We describe neurological features, laboratory tests, electrophysiological exams and pathological findings of the patient.

Results:
We report a thirty-eight-year-old man with asymmetric numbness and weakness of limbs for two months. The patient had intermittent numbness of the left foot and right hand two months ago. A month later, persistent numbness, weakness and changes in skin color of the left foot and right hand developed.Hyperpigmentation on the limbs were observed. Streng was 4/5 in the right finger flexion and abduction and 4/5 in the left ankle and toe dorsiflexion. Diminished pinprick and temperature sensation in the radial side of the hands and below the left ankle were noted. Deep tendon reflexes were normal. Nerve conduction studies showed a mononeuritis multiplex axonal neuropathy. Qualitative serum cryoglobulinserum test were positive, and IgM-kappa was detected by immunofixed electrophoresis. Rheumatoid factor was elevated at 814.9IU/ML. C4 complement was reduced at 0.087g/L. The hepatitis B viral load was elevated at >1.0*108IU/ML. Lymphoproliferative diseases including bone marrow biopsy and flow cytometry revealed very a low percentage of abnormal plasma cells (0.5% and 0.18%). Sural nerve biopsy suggested axonal damage and active vasculitis. A diagnosis of cryoglobulinemic neuropathy associated with HBV was made. The patient was treated with antiviral therapy with entecavir and immunosuppressive treatment with glucocorticoid. Numbness and weakness were nearly resolved.

Conclusions:
In conclusion, we report a case of HBV related Cryoglobulinemic Neuropathy, successfully treated with combined therapy of antiviral and glucocorticoid.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Cryoglobulinemic Neuropathy, HBV

Changes in PBMCs and serum following different methods of apheresis in patients with immune mediated neurological diseases

Poster No:
P 464

Authors:
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Institutions:
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Introduction:
Immune-mediated neurological diseases, such as Chronic lnflammatory Demyelinating Polyneuropathy (CIDP), Guillain-Barre syndrome (GBS) and Multiple Sclerosis (MS) are characterized by axonal or myelin damage due to autoimmunological processes. Therapeutic apheresis is a commonly used therapy, that removes pathogenic agents such as autoantibodies, inflammatory cytokines or complement from the patient's blood. Although clinically relevant, it is not yet known whether different methods of apheresis, namely plasma exchange (PE) and immunoadsorption (IA), do have a specific impact on protective and destructive serum factors as well as on clinical outcome parameters.

Methods:
Patients with immune mediated neurological conditions (CIDP, GBS, MS; n=75) and controls (n=16) before, during and after apheresis therapy were included. Pro- and anti-inflammatory cytokines, neurotrophic factors, hormones, and vitamins were measured in in patient's blood samples. Immune cell subpopulations were determined using flow cytometry. Clinical and electrophysiological parameters were evaluated.

Results:
The preliminary results show a correlation between the therapeutic procedures and a wide variety of pro/anti-inflammatory and destructive/protective factors. In particular, the first apheresis effectively eliminates immunogenic plasma factors, with PE being more effective than IA. Blood pressure drops occur with both procedures but are more severe with PE. Hemoglobin and fibrinogen also decrease more with PS than with IA. However, IA preserves more vitamins and may even increase serum levels of hepatocyte growth factor (HGF) and IL-10 – considered to be neuroprotective and anti-inflammatory - compared to PE.

Conclusions:
PS eliminates plasma proteins but also neuroprotective factors more strongly than IA. Overall, patients with IA had fewer side effects. A better understanding of the effects caused by different apheresis methods may help to improve patient's outcome regarding a specialized therapy dependent on patients' characteristics. Some may benefit from a more specific removal of destructive factors while others may rely on the preservation of protective and regenerative factors in an acute therapy for inflammatory conditions in neurology.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Therapeutic apheresis, CIDP, GBS, immunadsorption, Plasma exchange

High-dose biotin neither fosters remyelination nor stimulates malonyl-coA synthesis in the regenerating nerve

Poster No:
P 465

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Introduction:
Biotin is an essential cofactor for five carboxylase enzymes, including acetyl-CoA carboxylase (ACC). Given the involvement of these carboxylases in a wide range of metabolic pathways, it has been hypothesized that supraphysiological doses of biotin might have neuroprotective and regenerative potential. For example, treatment with high-dose biotin (HDB) might contribute to ATP production by increasing intermediates of the TCA cycle and may improve remyelination by elevating levels of the ACC product, malonyl-CoA, as a building block for fatty acid synthesis. However, these claims regarding the presumptive mode of action of HDB in humans have barely been validated in preclinical studies employing appropriate animal models.

Methods:
To decipher the impact of HDB on peripheral nerve regeneration, we performed sciatic nerve crush in wildtype C57BL/6 mice treated with 60 mg/kg biotin daily (corresponding to human equivalent dose of 300 mg). Animals were monitored over the course of 21 days and subjected to clinical testing by grip strength analysis, hemogram profiles and finally morphometric assessment. Additionally, at 14 days post-crush, sciatic nerve malonyl-CoA was quantified.

Results:
We were able to detect highly significant increases in malonyl-CoA during nerve regeneration in both vehicle and HDB-treated mice. However, there was no additional improvement under HDB-treatment. In line with this, we did not find HDB to enhance performance in the grip strength test. Coherently, morphometric analysis revealed no impact on myelin thickness or axonal diameter distribution. Hemogram profiles were unremarkable.

Conclusions:
Collectively, our findings strongly suggest that HDB is not effective in promoting peripheral nerve regeneration and that HDB does not modulate the activity of its proposed target – namely ACC and malonyl-CoA production. This functional lack in the PNS may explain why it apparently cannot promote regeneration in the CNS, as indicated by a recent phase 3 clinical trial on HDB in progressive multiple sclerosis, which failed to reach its endpoints.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Biotin, Nerve Injury, Nerve crush, Remyelination, Regeneration

Nerve ultrasound score in chronic inflammatory demyelinating polyneuropathy

Poster No:
P 466

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Introduction:
Studies have suggested that by applying certain nerve ultrasound scores, demyelinating and axonal polyneuropathies can be differentiated. In the current study, we investigated the utility of ultrasound pattern sub-score A (UPSA) in the diagnostic evaluation of demyelinating neuropathies.

Methods:
Nerve ultrasound were performed in patients with chronic inflammatory demyelinating polyneuropathy (CIDP) and acute inflammatory demyelinating polyneuropathy (AIDP); and compared to patients with axonal neuropathies. The UPSA, i.e. the sum of ultrasound scores at 8 predefined measurement points in median (forearm, elbow and mid-arm), ulnar (forearm and mid-arm), tibial (popliteal fossa and ankle) and fibular nerve (lateral popliteal fossa) were applied.

Results:
34 CIDP, 15 AIDP and 16 axonal neuropathies including eight axonal Guillain-Barré syndrome (GBS), four hereditary transthyretin amyloidosis, three diabetic polyneuropathy and one vasculitic neuropathy were included. 30 age- and sex-matched healthy controls were recruited for comparison. Significantly enlarged nerve cross-sectional areas (CSA) were seen in CIDP and AIDP, with the degree of enlargement by UPSA more significant in CIDP compared to the two groups (9.9 ± 2.9 vs 5.9 ± 2.0 vs 4.6 ± 1.9 in AIDP vs axonal neuropathies, $p < 0.001$). 89.3% of the CIDP patients had UPSA score ≥ 7 compared to AIDP (33.3%) and axonal neuropathies (25.0%) ($p < 0.001$). The performance of UPSA in determining CIDP was excellent (area under the curve of 0.943) with high sensitivity (89.3%), specificity (85.2%) and positive predictive value (73.5%).

Conclusions:
The UPSA ultrasound score was useful in distinguishing CIDP from other neuropathies compared to nerve CSA alone.

References:
Yes

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Grimm A, Heiling B, Schumacher U, Witte OW, Axer H. Ultrasound differentiation of axonal and demyelinating neuropathies. Muscle Nerve 2014;50:976-83.

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References 4:
Grimm A, Décard BF, Axer H, Fuhr P. The Ultrasound pattern sum score – UPSS. A new method to differentiate acute and subacute neuropathies using ultrasound of the peripheral nerves. Clin Neurophysiol 2015;126:2216-25.

Grant Support:

Keywords: Acute inflammatory demyelinating polyneuropathy, Chronic inflammatory demyelinating polyneuropathy, Guillain-Barré syndrome, Nerve ultrasound, Ultrasound pattern sum score

Analysis of gait patterns in patients with peripheral neuropathies using a novel wearable system

Poster No:
P 467

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Introduction:
Objective outcome measures monitoring clinical status and response to treatment in peripheral neuropathies patients are lacking. Wearable sensors analyzing motion are available for objective gait assessment and were successfully used to monitor gait and balance in patients with other neurological diseases. This technology allows to measure biomechanical parameters that are informative of the patient's clinical status and may also be useful to monitor disease activity. In this study we used a new wearable system to assess gait patterns in a cohort of patients with peripheral neuropathies.

Methods:
We performed a transversal study analyzing gait parameters in patients with immune-mediated neuropathies, CMT and healthy controls. Patients were classified by a neurologist based on their gait pattern in the following groups:1.steppage,2.gait ataxia,3.normal gait. We used the Ephion Mobility system that registers and integrates data from multiple wearable inertial sensors placed at different locations (feet, ankles, thigh, and chest), surface EMG integrated in shorts and plantar insoles. This system allows measuring kinematics, spatio-temporal parameters, plantar pressure, muscle activation and heart rate. Individuals wore the wearable system while performing the 2-minute walking test.

Results:
We included 21 CIDP patients,14 IgM-MGUS-associated neuropathies,7 CMT patients and 28 controls. Significant differences were observed in the gait speed, cadence, stance and swing and double support duration between patients and healthy controls. Moreover, we found differences between patients with steppage, gait ataxia and normal gait in the plantar pressure data and ankle and hip angles during the gait cycle. These results will be presented at the meeting.

Conclusions:
The Ephion Mobility system is an easy-to-use tool to objectively monitor gait in patients with peripheral neuropathies. We captured significant differences between steppage, gait ataxia and normal gait groups in this transversal study. Longitudinal studies are needed to identify if this novel system can capture disease and response to treatment status over time.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Peripheral neuropathies, Wearable Devices , Outcome Measure and Cinimetrics, CIDP

Characteristics of Guillain-Barré syndrome with takotsubo cardiomyopathy

Poster No:
P 468

Authors:
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Institutions:
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Introduction:
Autonomic dysfunction is observed in approximately two-thirds of patients with Guillain-Barré syndrome (GBS). Takotsubo cardiomyopathy (TCM) which is possibly caused by the dysfunction of sympathetic nervous system is a rare complication in GBS. In the present study, we investigated the characteristics of GBS with TCM (GBS-TCM).

Methods:
We retrospectively collected the clinical and serological information of GBS-TCM patients whose sera were tested for anti-glycolipid antibodies at our institutions from January 1, 2013 to December 31, 2020. We also compared the clinical features and anti-glycolipid antibodies of GBS-TCM with those of 62 patients with classical GBS without TCM who met Brighton's criteria for level 1 or 2 as control GBS patients.

Results:
GBS-TCM was found in eight patients, and TCM was diagnosed at 6.5 [3-42] days after onset of GBS. Six of eight were females, and age at onset was older in GBS-TCM (76.5 [56-87] vs. 52 [20-88] years, $p<0.01$). Six had preceding events (respiratory infection in four, gastrointestinal infection in one, and fever in one). Notably, cranial nerve deficits especially in lower cranial nerves were seen in all (100% vs. 41.9%, $p<0.01$). Additionally, GBS disability score at nadir was higher (5 [4-5] vs. 4 [1-5], $p<0.01$) and Medical Research Council sum scores at admission and nadir were lower (37 [30-44] vs. 48 [12-60] at admission and 20 [12-44] vs. 40 [0-60] at nadir, $p<0.05$, respectively). Mechanical ventilation was more frequently required in GBS-TCM (62.5% vs. 11.3%, $p<0.01$). According Ho's criteria, nerve conduction study exhibited acute inflammatory demyelinating polyneuropathy in four, acute motor axonal neuropathy in one, and unclassified in three. Three were positive for anti-glycolipid IgG antibodies.

Conclusions:
TCM occurred at relatively early phase in GBS-TCM. The characteristics of GBS-TCM (the elder, lower cranial nerve involvement, severe limb weakness, and respiratory failure) were clarified.

References:

No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Guillain-Barré syndrome, takotsubo cardiomyopathy, anti-glycolipid antibody

Soluble Interleukin-2 Receptor Levels Are Associated With The Clinical Course And Outcome In Guillain-Barré Syndrome

Poster No:
P 469

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Institutions:
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Introduction:
The soluble interleukin-2 receptor (sIL-2R) is released from activated T-cells and commonly used in clinical practice to monitor disease activity in various systemic auto-immune diseases. In Guillain-Barré syndrome (GBS) the role of T-cell activation has not been clarified, but previous small-scale studies indicated that sIL-2R levels are elevated in GBS and associated with the disease course. The aim of this study was to determine longitudinal serum sIL-2R levels in relation to preceding infections, clinical course, treatment response, and outcomes in patients with GBS.

Methods:
Acute-phase and follow-up sera from 289 patients with GBS and sera from 75 healthy controls were tested for sIL-2R levels with enzyme-amplified chemiluminescence immunoassays. Included patients previously participated in the randomized placebo-controlled trial to determine the effect of a second intravenous immunoglobulin dose (SID-GBS trial). Standard serological follow-up time points were 1, 2, 4, and 13 weeks. Clinical features were analyzed in relation to longitudinal sIL-2R levels.

Results:
Study entry samples from patients showed higher serum sIL-2R levels (median: 433, IQR: 315-684) compared to controls (median: 306, IQR: 259-404). High levels at entry (>552) persisted for at least 3 months in most patients (38/62) and were associated with positive serology for cytomegalovirus, Epstein-Barr virus, or hepatitis E virus and lower Medical Research Council sum scores at 1, 2, and 4 weeks. Moreover, these patients required more time to regain the ability to walk unaided and the ability to run, and less often regained the latter. These associations remained after correcting for known clinical prognostic factors.

Conclusions:
Serum sIL-2R levels are increased in the acute phase of GBS and high levels are associated with preceding viral infections, more severe clinical disease, and poor outcome. These findings suggest that excessive T-cell activation occurs in at least a proportion of patients with GBS, which may potentially play a role in the pathophysiology.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Guillain-Barré syndrome, Biomarkers, Soluble interleukin-2 receptor, Prognosis

Siponimod Improve Experimental Autoimmune Neuritis in Lewis Rats

Poster No:
P 470

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Introduction:
Siponimod (S) acts on sphingosine-1-phosphate receptor1(S1PR1) to inhibit lymphocyte migration. It has shown efficacy on multiple sclerosis as a disease modifying drug. However, its efficacy against autoimmune peripheral neuropathy remains unclear. Herein, the effect of siponimod on experimental autoimmune neuritis (EAN) was examined.

Methods:
7-week-old female Lewis rats were immunized with synthetic peptide of bovine P2 protein. Five to 27 days 5 to 27 sfter immunization, rats in the S group were orally administered 1.0mg/kg of S and rats in the EAN group were orally received PBS only. Motor disability was assessed daily using 9-grade scale. At days(D) 5, 9, 12, 15, 21 and 28 post immunization (p.i.), popliteal lymph nodes (LN) and cauda equina (CE) were collected after thorough perfusion using cool PBS. We investigated mRNA expression of interferon gamma (IFN) and IL-10 in LN and CE by real-time PCR. Additionally, in CE, gene expression involved in peripheral nerve regeneration (c-Jun, Shh) were examined similarly. For histological study, sections of CE were stained by H&E and LFB.

Results:
Motor paralysis peaked at D14-16 p.i., significantly mild in siponimod group during entire course. Histologically, cell infiltration and demyelination correlated with motor paralysis. In EAN LN, IFN peaked at D9 p.i., and IL-10 peaked at D15 p.i. S suppresses these expression. In EAN CE, IFN peaked at D12 p.i. and IL-10 peaked at D 15 p.i., whereas they showed only moderate peaks in S group. c-Jun and Shh increased at D12~28 p.i. especially in S group.

Conclusions:
S inhibited EAN clinically and histologically. That siponimod inhibited IFN but did not facilitate IL-10 indicates Th1 suppression is its main arm. S probably stimulate c-Jun and Shh expression during recovery stage, suggesting activating remyelination. S might be an optional treatment for autoimmune neuritis.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: demyelinating polyneuropathy experimental autoimmune neuritis, siponimod, S1PR1, S1PR5

Changes in Patient Reported Outcome Measures After SARS-CoV-2 Vaccinations In Patients With Autoimmune Neuromuscular Disease

Poster No:
P 471

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Introduction:
In patients with autoimmune neuromuscular disease, concerns exist about increased disease activity after vaccination. We assessed changes in patient reported outcome measures (PROMS) after SARS-CoV-2 vaccination in these patients.

Methods:
Substudy of a prospective observational cohort study (T2B!). Patients with autoimmune neuromuscular diseases who received SARS-CoV-2 vaccination were included. Patients completed PROMS, before and 60 days after first vaccination. For myasthenia gravis (MG) the MG activities of daily living (MG-ADL) was used, for CIDP the Inflammatory Rasch-built Overall Disability Scale (I-RODS), for MMN the RODS (MMN RODS), and for inflammatory myopathies the Health Assessment Questionnaire-Disability Index (HAQ-DI). PROMS were compared before and after vaccination and we assessed the proportion of patients deteriorating at least the minimal clinically important difference (MCID) for MG and CIDP.

Results:
We included 230 patients (mean age 54.3 years [SD 13.3], 123 (54%) female sex), of which 123 (54%) with MG, 42 (18%) with CIDP, 25 (11%) with MMN and 40 (17%) with inflammatory myopathies. Median scores on each of the PROMS did not change after vaccination; MG-ADL 3 (IQR 1–6) vs. 3 (IQR 1–5), p=0.36; I-RODS 40.0 (IQR 35.3–44.8) vs. 41.0 (IQR 36.0–44.8), p=0.70; MMN RODS 45.0 (IQR 42.0–49.0) vs. 44.0 (IQR 39.0–48.0), p=0.61; HAQ-DI 0.69 (IQR 0.13–1.13) vs. 0.50 (IQR 0.22–1.16), p=0.77. Deterioration of at least the MCID occurred in 17 of 123 (14%) MG patients (i.e. 2 points), and 5 of 42 (12%) CIDP patients (i.e. 4 points). Three out of 22 (14%) patients with deterioration reported an adjustment in their treatment.

Conclusions:
No significant changes in disease activity on group level were observed after SARS-CoV-2 vaccination. If deterioration occurred, this was only minor because treatment changes were reported rarely. Our study indicates that SARS-CoV-2 vaccination is safe in patients with autoimmune neuromuscular disease.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Disease activity, SARS-CoV-2 vaccination, Inflammatory neuropathies, Myasthenia gravis, Inflammatory myopathies

Clinical and epidemiological characteristics of the IMAGiNe patient cohort

Poster No:
P 472

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Introduction:
In a subset of polyneuropathy patients, polyneuropathy is a result of IgM M-proteins acting as antibodies on peripheral nerve components, with the myelin associated glycoprotein (MAG) as the most frequent target. Despite IgM-antibody related polyneuropathy being known for decades, consensus on the natural disease course, best treatment and treatment response measurement is lacking.

Methods:
In order to improve this, an international observational prospective cohort study was initiated in 2016 in the Netherlands; the IMAGiNe (IgM ± Anti-Myelin Associated Glycoprotein [MAG] peripheral Neuropathy) study. The IMAGiNe study aims to collect clinical, epidemiological and pathological data from patients in a standardized manner, with a follow-up period of 3 to 5 years. Investigations include questionnaires, neurological examination and laboratory tests. Additionally, patient material is collected in a biobank.

Results:
The data collected will be used to investigate the natural disease course and to create an IgM-polyneuropathy specific linearly weighted disability assessment scale with the Rasch methodology: the IgM-RODS.

Conclusions:
A large number of patients in different centers has reached a follow-up period of 36 months. In this article, we therefore present data on the baseline characteristics and the patterns and variability of the disease course of these patients.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Polyneuropathy, Myelin-associated glycoprotein, RODS, IMAGiNe, Inflammatory neuropathy

Signs of Demyelination and Axon Loss in Patients with Typical Chronic Inflammatory Demyelinating Polyneuropathy and Variants

Poster No:
P 473

Authors:
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Introduction:
The diagnosis of chronic inflammatory demyelinating polyneuropathy (CIDP) depends on clinical, electrodiagnostic and supportive criteria. The 2021 EAN/PNS guideline introduced clinical definitions of typical CIDP and CIDP variants, including multifocal, motor, distal, and sensory CIDP. Diagnosis is often delayed in CIDP variants, which could be partly attributed to differences in nerve conduction studies (NCS). Our objective was to compare signs of demyelination and axonal loss as assessed with NCS in typical CIDP and variants.

Methods:
Adults who underwent uniform extensive NCS in a tertiary referral center in Amsterdam between 2009 and 2019 were screened. Patients were selected if they either met the 2021 EAN/PNS electrodiagnostic criteria for (possible) CIDP, or did not meet the criteria, but CIDP remained to be the most likely diagnosis after 6 months and responded to treatment or met ≥2 other supportive criteria. NCS were reassessed using the 2021 EAN/PNS guideline. Signs of demyelination were not assessed when the distal compound muscle action potential (CMAP) amplitude was <1 mV. Low-amplitude and absent distal CMAPs and sensory nerve action potentials (SNAPs) served as indirect measures of axonal loss.

Results:
After screening, 142 patients were included, consisting of typical (n=92), multifocal (n=30), distal (n=6), motor (n=10), and sensory (n=4) CIDP patients. Signs of demyelination in typical CIDP were mostly found in the ulnar and median nerve and less often in the radial and musculocutaneous nerve. Low CMAP amplitudes were most frequent in the legs, but also found in the arms. In multifocal CIDP, fewer signs of demyelination were observed, but with the same nerve distribution as in typical CIDP. Low CMAP amplitudes were also less common than in typical CIDP, especially in the legs. Low-amplitude and absent SNAPs were less common in multifocal and motor CIDP.

Conclusions:
There are different patterns of signs of demyelination and axon loss between typical CIDP and CIDP variants.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: CIDP, EMG, NCS, Demyelination, Axon loss

The Effects of Implementing the European Academy of Neurology/Peripheral Nerve Society Guideline (second revision) on Diagnosis and Treatment of CIDP

Poster No:
P 474

Authors:
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Introduction:
The diagnosis of chronic inflammatory demyelinating polyneuropathy (CIDP) depends on a combination of clinical, electrodiagnostic, imaging and laboratory features. In 2021, the European Academy of Neurology/Peripheral Nerve Society (EAN/PNS) guideline (second revision) was published, replacing the 2010 European Federation of Neurological Societies/Peripheral Nerve Society (EFNS/PNS) guideline. In the revised guideline, the diagnostic categories were reduced from three (definite, probable, possible CIDP) to two (CIDP, possible CIDP). Definitions of CIDP variants were added, and the electrodiagnostic criteria were revised. The objective is to compare the diagnostic yield of the 2021 guideline with the 2010 guideline.

Methods:
We included patients who fulfilled the 2010 EFNS/PNS electrodiagnostic criteria for possible, probable or definite CIDP, treated at one of three tertiary referral centers for CIDP. Additionally, we included patients who did not meet the 2010 EFNS/PNS electrodiagnostic criteria, but for whom CIDP was still the most likely diagnosis based on clinical evaluation, ≥1 supportive criterion, and treatment response. These two groups combined were considered as the reference standard. The control group consisted of patients who underwent extensive nerve conduction studies based on suspicion of having CIDP or multifocal motor neuropathy, but received an alternative diagnosis after diagnostic work-up or follow-up. The sensitivity and specificity of the 2021 EAN/PNS criteria were compared to the combined reference standard.

Results:
At present, 225 patients from two hospitals have been included. Of the 198 patients who fulfilled the probable or definite 2010 criteria, 154 (77.8%) also fulfilled the 2021 criteria. Of the 21 patients who did not fulfill the 2010 criteria, but for whom CIDP was considered the most likely diagnosis, one (4.8%) fulfilled the 2021 criteria for CIDP. Final results, including specificity, will be presented at the conference after adding patients from the third hospital and the patient-control group.

Conclusions:
Preliminary results suggests that the sensitivity of the revised guideline is slightly lower.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: CIDP, EMG, Diagnostic criteria, Sensitivity

Pharmacometric analysis of intravenous immunoglobulin treatment in patients with the Guillain-Barré syndrome

Poster No:
P 475

Authors:
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Introduction:
Response to intravenous immunoglobulin (IVIg) treatment in patients with Guillain-Barré syndrome (GBS) is highly variable. Recently, we developed the first pharmacokinetic (PK) model for standard IVIg treatment in patients with GBS (1). In this study, we aim to evaluate the robustness of the PK model for GBS patients receiving multiple IVIg dosing regimens, and define the relationship between IVIg PK and clinical outcome, ultimately moving towards precision dosing of IVIg in GBS patients.

Methods:
Data was derived from patients participating in the second IVIg dose (SID)-GBS trial, in which patients with a poor prognosis were randomized for a SID or placebo. The model was externally evaluated with diagnostic plots and visual predictive checks using non-linear mixed effect modelling. The root mean square error and mean prediction error were computed to assess precision and bias, respectively. Monte Carlo simulations were performed to obtain individual concentration-time curves.

Results:
Ninety randomized patients were included with a total of 339 serial serum IgG levels taken at 0, 2, 4, 12, and 26 weeks. Of these patients, 49 were randomized to a second IVIg course, and 41 received placebo. Visual predictive checks stratified by treatment arm showed that the median and variability of the observations fell within the model-predicted boundaries, which indicates that the model also accurately predicts the PK after multiple IVIg courses. Predicted values were not biased (MPE = -0.28) and good precision was observed (RMSE = 10.4%). Further details on the relationship between the PK of IVIg (exposure, Cmax, delta IgG) and clinical outcome will be presented at the PNS annual meeting.

Conclusions:
This study shows that the PK model for IVIg also accurately predicts IgG levels after multiple IVIg courses. The model can be used to link the PK of IVIg to the pharmacodynamics in individual patients with GBS, and may lead to personalized dosing regimens.

References:
Yes

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Fokkink WJR, van Tilburg SJ, de Winter BCM, et al. Population Pharmacokinetic Modelling of Intravenous Immunoglobulin Treatment in Patients with Guillain-Barré Syndrome. Clin Pharmacokinet. 2022;61(9):1285-1296. doi:10.1007/s40262-022-01136-z

References 2:

References 3:

References 4:

Grant Support:

Keywords: Intravenous immunoglobulin, Pharmacokinetics, Pharmacodynamics, SID-GBS trial

F-wave abnormalities associated with motor conduction block

Poster No:
P 476

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Introduction:
To evaluate alterations in F-wave parameters in nerves with motor conduction block (CB) occurring in different neuropathies.

Methods:
We automatically analyzed 40 consecutive F-waves in 20 patients with ulnar nerve CB (9 males, mean age 54.3 ± 18.9 years) and 20 patients with peroneal nerve CB (16 males, 52.0 ± 18.2 years). Each group consisted of 5 acute inflammatory demyelinating polyneuropathy (AIDP), 5 acute motor axonal neuropathy (AMAN), 5 chronic inflammatory demyelinating polyneuropathy (CIDP) and 5 entrapment mononeuropathy (MN) patients.

Results:
Temporal dispersion (TD) in addition to CB was identified in 7/20 ulnar and 5/20 peroneal nerves, in all conditions except AMAN. F-wave persistence (mean ± SD) was variably reduced in both nerves, ranging from 5.5 ± 8.7% in AMAN to 73.0 ± 17.9% in CIDP for the ulnar nerve, and from 5.5 ± 12.3% in AIDP to 30 ± 31.7% in AMAN for the peroneal nerve. However, repeater F-waves (Freps) frequency, expressed as Index Total Freps (100 x total number of Freps/ total number of traces with F-waves), was similarly increased in all studied conditions in both nerves. A subanalysis showed significant prolongation in minimum F-wave latencies and F chronodispersion only in predominantly demyelinating disorders i.e. AIDP and AMAN, regardless of abnormal TD. F-wave latency measurements were normal in AMAN and MNs.

Conclusions:
In nerves with CB, with or without abnormal TD, abnormalities in F-wave latency measurements are indicative of an underlying demyelinating procedure. Abnormally increased Index Total Freps is the only parameter invariably related to CB irrespective of the underlying pathology.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: F-waves, Repeater F-waves, Conduction block, Neuropathies

Chronic Inflammatory Demyelinating Polyneuropathy: A Comparative Study On Magnetic Resonance Neurography and High-resolution Nerve Ultrasound

Poster No:
P 477

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Introduction:
Background: Magnetic Resonance Neurography (MRN) and High-resolution nerve ultrasound (HRUS) are evolving, complimentary diagnostic modalities in Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). There have been few studies comparing the correlation of nerve Cross-sectional area (CSA) by HRUS and MRN and their correlation with electrophysiology. Objectives: a) To compare HRUS and MRN in CIDP and to compare with age and sex matched controls b) To correlate imaging parameters, disease severity and electrophysiological parameters in CIDP

Methods:
Prospective, cross-sectional study from June 2020 till February 2022. 20 patients with typical CIDP fulfilling EFNS/PNS criteria and 20 age and sex-matched controls were included. Patients underwent MRN, HRUS and electrophysiological studies.

Results:
The mean age at onset was 39.31 ± 15.13 (18.5-64.75 years) and at presentation was 40.12 ± 14.9 (19-65). The mean duration of progression of the illness was 4.4 ± 2.58 months Male: female- 12:8. INCAT disability score ranged 1-8. The median, lower and upper quartiles of CSA of the trunks of the brachial plexus by HRUS and MRN were: Right superior trunk- 0.13 (0.07,017)/0.13 ((0.08,0.18), right middle- 0.13(0.11,0.16)/ 0.13(0.11,0.16), Right inferior - 0.13(0.09,0.20)/ 0.13(0.10,0.20), Left superior - 0.11(0.08,0.15)/ 0.12(0.08,0.16), Left middle- 0.14(0.12,0.20)/ 0.14(0.12,0.21),left inferior - 0.14(0.10,0.17)/ 0.15(0.11,0.17). The CSA of controls by HRUS and MRN ranged 0-06 and 0.07. Spearman's correlation had significant correlation between HRUS and MRN in cases and controls. Mann-Witney test showed significant variation in CSA between cases and controls by both MRN and HRUS. Distal latency of nerves showed non-significant positive correlation while amplitude, conduction velocity and f wave persistence showed non-significant negative correlation with CSA. INCAT disability score had positive non-significant correlation with CSA.

Conclusions:
MRN and HRUS show significant differences in CSA of brachial plexus trunks between patients and controls and have significant correlation with each other. CSA also has non-significant correlation with electrophysiological parameters.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: Nil

Keywords: Magnetic resonance neurography, High resolution ultrasound, Chronic inflammatory demyelinating polyneuropathy

Acute Intermittent Hypoxia, A Novel Therapy To Enhance Regeneration Of Severely Compressed Nerves Following Decompression

Poster No:
P 478

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Introduction:
Severe nerve compression injuries are common and can lead to loss of function and debilitating pain states. While direct median nerve electrical stimulation (ES) improves functional recovery in severe carpal tunnel syndrome in humans (sCTS), this approach is invasive. We have shown a novel non-invasive therapy called acute intermittent hypoxia (AIH) promotes regeneration of co-apted rat tibial nerves in a manner akin to ES. But, whether it does so in decompressed nerves has not been examined, nor has the capacity for AIH to prime/enhance early regeneration when delivered prior to decompression been assessed.

Methods:
To evaluate the capacity for AIH to improve repair of severely compressed nerves following decompression, we developed a reproducible and precise nerve compression and decompression preclinical model that mimics sCTS pathology. Injuries were performed using a mechanical force gauge sensor linked to a data acquisition system, allowing reproducible and consistent unilateral severe sciatic compression injuries in adult male Lewis rats with 14 grams of force on each of 4 constriction sites spanning 3mm. Fourteen days post-injury, nerves were decompressed, and early regeneration assessed one week later. A single AIH treatment consists of 10 cycles of 5 minutes 11% O2 alternating with 5 minutes 21% O2.

Results:
Data support that a single priming AIH treatment (pAIH) 7d prior to decompression is most effective at enhancing the numbers of axons and distance of regeneration relative to Normoxia controls (21% O2) with improvements also observed in response to pAIH+7d daily AIH post-compression or 7d daily AIH post-decompression. Additionally, this compression model induced a hyposensitivity, which improved within 7d post-decompression in all 3 AIH treatment protocols. Ongoing experiments are assessing impact of AIH on reinnervation, the distal nerve environment and functional/behavioral outcomes.

Conclusions:
Collectively, the data support that non-invasive AIH therapy promotes improved nerve repair outcomes following nerve decompression.

References:
Yes

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Gordon T, Amirjani N, Edwards DC, Chan KM. Brief post-surgical electrical stimulation accelerates axon regeneration and muscle reinnervation without affecting the functional measures in carpal tunnel syndrome patients. Exp Neurol. 2010;223(1):192-202.

References 2:
Nadeau JR, Arnold BM, Johnston JM, Muir GD, Verge VMK. Acute intermittent hypoxia enhances regeneration of surgically repaired peripheral nerves in a manner akin to electrical stimulation. Exp Neurol. 2021;341:113671.

References 3:

References 4:

Grant Support: Research supported by a Canadian Institutes of Health Research grant #063-25663 to VMKV and KMC and a UofS CoMRAD grant to VMKV

Keywords: nerve regeneration, acute intermittent hypoxia, nerve compression injury, nerve decompression, therapy

Endocrine Changes Observed in Patients With Guillain-Barré Syndrome (GBS) And The Relationship With Severity

Poster No:
P 479

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Introduction:
Acute and chronic phases of a critical illness are likely to be two distinct neuroendocrine paradigms. GBS can be a critical illness in some patients.

Methods:
A prospective study was carried out including all GBS patients who fulfilled the Brighton criteria, admitted to national hospital of Sri Lanka over 10 months. Details on demographics, clinical presentation, investigations, and treatment were obtained. Blood was tested for basic hematology, biochemistry, and endocrine parameters. The results were analyzed using SPSS and compared between mild and severe groups according to the mRS score.

Results:
Forty-nine patients who fulfilled the Brighton criteria for diagnosis of GBS were included in the study. Out of them 27 were males (55.1%). The mean age was 55 years. On nerve conduction study, 65.9% had AIDP, 20.5% had AMAN and 13.6% had non-specific F wave abnormalities. A 28.6% had mild disease and 71.4% had severe disease. Out of the statically significant parameters, mean serum albumin level was 19.17 g/dL, and inversely corelated with the severity of disease. (Pearson correlation -0.548, <0.01). Mean serum 9 am cortisol level of the total population was 452.9 nmol/L and showed direct correlation with severity of disease (Pearson correlation-0.534, <0.01). There was a significant difference between the means of mild and severe groups. In males, mean testosterone level was 168.80 ng/dL and showed a significant inverse correlation with the severity of disease [Pearson correlation -0.657, <0.01) p=0.008]. There was no correlation observed between the age and severity. In females there was no significant difference in sex hormone results between the groups.

Conclusions:
There is no literature available on detailed endocrine changes in GBS other than SIADH. There is significant alteration in serum cortisol level in total population and testosterone level in males related to severity. The changes observed need to be evaluated further especially regarding any effect on the recovery process.

References:
Yes

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References 3:
The Italian Guillain-Barré Study Group. The prognosis and main prognostic indicators of Guillain-Barre syndrome. A multicentre prospective study of 297patients. Brain1996; 119:2053–61.

References 4:

Grant Support:

Keywords: Guillain- Barre Syndrome, Endocrine changes, Severity , Low Testosterone

Clinical and temporal profile in management of chronic inflammatory demyelinating neuropathy (CIDP) and CIDP variants: A cohort study

Poster No:
P 480

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Introduction:
Chronic inflammatory demyelinating polyneuropathy (CIDP) is the most common chronic immune-mediated inflammatory polyneuropathy. According to latest EAN/PNS guideline, CIDP is classified into typical CIDP and CIDP variants. In this study, we describe a large cohort of CIDP and CIDP variants from a tertiary care centre in India.

Methods:
All patients clinically and electrophysiologically diagnosed as CIDP from Jan 2015 to December 2021 were included in the study. Demographic profile, clinical examination, laboratory and nerve biopsy findings, MRI, PET scan, management and follow up data were collected. The clinical disability was assessed using MRC, MRS, ODSS, NIS, IRODS, SCOPA AUT scales. Based on all available investigations, a final diagnosis of CIDP, CIDP variant or secondary CIDP were ascertained.

Results:
A total of 83 patients were included with the mean age of 47 (SD 15) years and male predominance (M:F 70:13). The median duration of disease was 3(IQR 4) years. 57 (69%) were typical CIDP, while variant CIDP constituted 26 (31%). MADSAM (n=8)(9.64%) was the most common CIDP variant. POEMS was the most common cause of secondary CIDP. Asymmetry was more in variant CIDP (65 % compared to 44 % in typical CIDP). The mean CSF protein (208) was raised in all patients of CIDP with significantly higher protein values (228) observed in typical CIDP compared to variant CIDP (159). 31% with variant CIDP underwent nerve biopsy to support the diagnosis compared to 19 % in the typical CIDP group. Among treatment received, typical CIDP had overall more need for PLEX and IVIG as compared to variant CIDP. Steroid was the most common therapy used in both groups. Most common steroid sparing drug used was Azathioprine. 10 patients died and 50% mortality was attributed to COVID19.

Conclusions:
We describe a large cohort of CIDP and CIDP variants from India including unique insights into clinical and management profiles.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: No

Keywords: Chronic inflammatory demyelinating polyneuropathy , CIDP Variant, Inflammatory neuropathy

Efgartigimod: Clinical Development of an FcRn Antagonist for Treatment of IgG-Mediated Autoimmune Neurological Diseases

Poster No:
P 481

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Introduction:
Immunoglobulin G (IgG) autoantibodies are thought to play a key role in the pathogenesis of many autoimmune diseases, including chronic inflammatory demyelinating polyneuropathy (CIDP), generalized myasthenia gravis (gMG), and idiopathic inflammatory myopathy (IIM). Neonatal Fc receptor (FcRn) recycles IgG, extending its half-life and serum concentration. Efgartigimod is a human IgG1 antibody Fc-fragment that blocks FcRn, outcompeting endogenous IgG binding, reducing IgG recycling, and increasing IgG degradation. Here we summarize evaluation of IgG reduction by efgartigimod in autoimmune neurological conditions.

Methods:
Several clinical trials of efgartigimod are completed or ongoing for a variety of autoimmune diseases. Initial approval for intravenous efgartigimod in gMG was supported by the 26-week, randomized, double-blind, placebo-controlled ADAPT trial evaluating efgartigimod (cycles of 4 weekly infusions) in adult patients (N=167). Select ongoing gMG studies include ADAPT-SC+, an open-label study evaluating long-term safety, efficacy, and tolerability of efgartigimod PH20 SC (coformulated with recombinant human hyaluronidase PH20) in adults, and ADAPT JR in pediatric patients. Other ongoing studies include ADHERE, an event-driven, phase 2 prospective trial investigating efficacy and safety of weekly dosing of efgartigimod PH20 SC in adult patients with CIDP. ADHERE will be completed in an open-label stage A and a randomized-withdrawal, double-blind, placebo-controlled stage B. Efficacy and safety of weekly dosing of efgartigimod PH20 SC is being evaluated in ALKIVIA, a phase 2 (24-week)/3 (52-week), randomized, double-blinded, placebo-controlled, parallel-group study in adult patients with IIM.

Results:
Across all completed studies to date, efgartigimod demonstrated consistent and repeatable reductions in total IgG (ranging between 61.3-71.2%), including pathogenic autoantibodies, which corresponded with clinical improvement. Efgartigimod was well tolerated, and adverse events were mostly mild to moderate.

Conclusions:
Therapeutic blocking of FcRn by efgartigimod is approved for the treatment of gMG and is a promising potential therapeutic option for several additional neurological diseases mediated by pathogenic IgG autoantibodies, including CIDP and IIM.

References:
Yes

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References 2:
Ulrichts P, et al. J Clin Invest. 2018;128(10):4372-4386.

References 3:
Wolfe GI, et al. J Neurol Sci. 2021;430:118074.

References 4:

Grant Support:

Keywords: FcRn-inhibition, CIDP, IIM, MG, Neurological autoimmune diseases

Clinical Features, Diagnostic Criteria And Response To Treatment Of Guillain-Barré Syndrome: A Series Of 21 Cases At Military Hospital 175

Poster No:
P 482

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Introduction:
Guillain Barré Syndrome is an acute or subacute polyradiculoneuropathy that often follows an upper respiratory tract infection or gastroenteritis by 10 to 14 days.

Methods:
To describe the clinical, electrodiagnostic features and treatment response characteristics of GBS patients in the 175 Military Hospital. This is a case series based upon the diagnostic criteria for CIDP diagnosis of NINDS (National Institute of Neurological Disorders and Stroke), modified in 2019. The patients were examined for all clinical symptoms and signs, electromyographic features, cerebrospinal features, and treatment response.

Results:
This review includes 12 GBS cases presenting subtype AIDP (Acute inflammatory demyelinating polyneuropathy), 5 GBS cases presenting subtype AMSAN (Acute Motor Sensory Axonal Neuropathy) and 4 GBS cases presenting subtype AMAN (Acute Motor Axonal Neuropathy). Preceding infections with almost an upper respiratory tract infection or gastroenteritis in 85% of cases. Seven cases (33%) had abnormal cranial nerves, 18 had a sensory disorder, and all had an absence of deep tendon reflexes. In laboratory results, 20 cases (95%) had a sural-sparing pattern in nerve conduction study. All cases received specific treatment, nine nous immunoglobulin therapy, and 12 received plasma exchange therapy. Eighteen cases (85%) improved and could walk independently after three months, and 20 (95%) could walk independently after six months. One case (5%) was a poor improvement after one year.

Conclusions:
Guillain Barré Syndrome is a treatable acquired peripheral neuropathy. The diagnosis of GBS is based on clinical history and examination and is supported by ancillary investigations such as cerebrospinal fluid examination and electrodiagnostic studies. Specific treatment is plasma exchange and immunoglobulin. The prognosis of the disorder is good; most cases can walk independently after six months.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Guillain Barré Syndrome, NINDS

Application of 18F-FDG PET/CT in Identifying Multiple Myeloma in Monoclonal Gammopathy Associated Peripheral Neuropathy

Poster No:
P 483

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Introduction:
Peripheral neuropathy is a well-recognized complication in plasma cell disorders, but a challenging clinical problem in terms of diagnosis and treatment. Routine procedures usually fail to make the underlying pathologic diagnosis. The purpose of this case presentation was to demonstrate the application of18F-FDG PET/CT image radiomics in the identification of the underlying causes of monoclonal gammopathy associated neuropathy.

Methods:
We describe neurological features, laboratory tests, electrophysiological exams, PET/CT scans, and pathological findings of the patient who was initially diagnosed with CIDP.

Results:
A 22-year-old man was initially noticed with numbness and weakness in his feet 2 years ago. Despite of short period of mild regression with intravenous methylprednisolone, the symptoms progressed to the knee and hands. Treatment of intravenous immunoglobulin and plasmapheresis was ineffective. Advanced laboratory evaluation confirmed the presence of IgG λ monoclonal(M) protein. Bone marrow biopsy from the iliac bone and flow cytometry were normal. Nerve conduction studies showed slowing of motor and sensory conduction velocities and conduction blocks in median and ulnar nerves. 18F-FDG PET/CT showed multiple hypermetabolic lesions in the vertebral bodies. Fluoroscopy-guided needle biopsy of a lumbar vertebral body confirmed the diagnosis of multiple myeloma (MM). He was subsequently given medication (lenalidomide, ixazomib, dexamethasone) and showed improvement in walking. Based on the clinical and electrophysiological features, positive M protein and pathological findings, as well as treatment response to myeloma therapy, a diagnosis of monoclonal gammopathy associated peripheral neuropathy was made.

Conclusions:
We present a case of monoclonal gammopathy associated peripheral neuropathy, diagnosed as MM by PET/CT and biopsy. We propose that PET/CT could be used as a reliable tool to a valuable tool for the work-up of young patients with monoclonal gammopathy associated neuropathy. A biopsy of a suspected lesion may help with early diagnosis.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Monoclonal Gammopathy Associated Peripheral Neuropathy, Chronic Inflammatory Demyelinating Polyneuropathy, 18F-FDG PET/CT, Multiple Myeloma, MGUS

Rituximab Treatment In Non-Systemic Vasculitic Neuropathy: A Danish Cohort Study

Poster No:
P 484

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Introduction:
Non-systemic vasculitic neuropathy (NSVN) is a vasculitis limited to the peripheral nerves. NSVN is considered an uncommon disease, but studies suggest that NSVN is more common than the inflammatory demyelinating polyradiculoneuropathies and is probably underrecognized. In 2010 The Peripheral Nerve Society established guidelines regarding diagnosis and treatment. In more recent literature Rituximab has been suggested as a possible treatment, but no study has investigated the efficacy of Rituximab in NSVN. The aim of this study was to evaluate the efficacy of treatment with Rituximab in a NSVN cohort from our Neuromuscular Center.

Methods:
19 patients with definite (2) or probable (17) NSVN treated with Rituximab were included in this retrospective observational cohort study. Rituximab was given in a fixed-dose regimen (1000 mg on day 1 and 15 and every 6 months for 2 years) in combination with 3 months of Prednisone 1 mg/kg and was initiated when the disease was actively progressing. Evaluation of the efficacy of treatment was based on a neurological examination performed by a physician and a test-battery performed by a physiotherapist at baseline and at follow-ups every 3 months. The neurological status is described as: Stable, worsened or improved compared to baseline.

Results:
Male/female ratio 9/10. The current status was: Improved n=4 (21%) (1 at 24 months, 3 patients at 12 months), stable n=6 (32%) (1 at 18 months, 2 at 9 months, 2 at 6 months and 1 at 3 months) and worsened n=1 (5%) (12 months). Discontinued n=4 (21%). Rituximab was generally well tolerated but 1 patient experienced severe adverse side-effects.

Conclusions:
Rituximab seems to be an efficient and safe treatment choice in progressive disease due to NSVN. Updated results and further clinical and paraclinical data will be presented at the upcoming PNS meeting.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: non-systemic vasculitic neuropathy, NSVN, immunosuppressive treatment, vasculitis, therapeutic outcome

Association between serum IgG antiganglioside antibodies and poor outcome in Guillain-Barré syndrome

Poster No:
P 485

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Introduction:
Approximately 20% of patients with Guillain-Barré syndrome (GBS) at 6 months from the onset remain to be unable to walk independently. Using modified Erasmus GBS outcome score (mEGOS), high score can predict such patients with poor outcome. We previously reported serum IgG-GD1a antibodies were associated with poor outcome and the combination of IgG-GD1a antibody positivity and high mEGOS could predict poor outcome more accurately than mEGOS alone. Recently Spanish group reported serum IgG-GM1 antibodies were associated with poor outcomes. This study aimed to validate whether serum IgG-GD1a antibodies or GM1 antibodies were associated with poor outcome in another GBS cohort.

Methods:
We retrospectively collected 334 GBS patients with any IgG antiganglioside antibodies examined in our laboratory. Poor outcomes were defined as ≥ 3 of GBS disability score at 6 months. Serum IgG antiganglioside antibodies were measured by ELISA.

Results:
Serum IgG-GM1 and GD1a antibodies were positive in 48% and 37% of 334 patients, respectively. We used multivariable logistic regression analysis to evaluate the relationships between IgG-GM1 or GD1a antibodies and poor outcomes. IgG-GD1a antibodies were independently associated with poor outcomes (OR 2.6, 95% CI: 1.24 to 5.31, p=0.01). In contrast, IgG-GM1 antibodies were not associated with poor outcomes. IgG-GD1a-positive patients significantly more frequently had poor outcomes than IgG-GD1a-negative patients (19% vs 9%, p=0.015). Patients with the combination of IgG-GD1a antibody positivity and high mEGOS (either on admission or on day 7) had poor outcomes at the rate of 55% and 59%.

Conclusions:
The presence of IgG-GD1a antibody, but not IgG-GM1 antibody, is independently associated with poor outcome.

References:
Yes

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References 2:
Walgaard C, et al. Neurology. 2011;76:968-975.

References 3:
Lleixà C, et al. J Neuroinflammation. 2021;18:251.

References 4:

Grant Support:

Keywords: Guillain-barré syndrome, Poor outcome, GD1a antibody, modified Erasmus GBS outcome score , GM1 antibody

CLINICAL AND ELECTRODIAGNOSTIC STUDY ON EARLY DIFFERENTIATION OF ACUTE-ONSET CHRONIC INFLAMMATORY DEMYELINATING POLYRADICULONEUROPATHY AND GUILLAIN-BA

Poster No:
P 486

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Introduction:
Acute-onset chronic inflammatory demyelinating polyradiculoneuropathy(CIDP) may be initially misdiagnosed as acute inflammatory demyelinating polyneuropathy (AIDP), a demyelinating variant of Guillain-Barré syndrome(GBS). Since treatment strategies differ between A-CIDP and AIDP, early differentiation between them is important. The purpose of this study is to identify early points of differentiation between A-CIDP and AIDP.

Methods:
Three A-CIDP patients (66 y/o female, 74 y/o female, and 53 y/o male) who received immunotherapy as AIDP within 2 weeks after the onset were and clinically and electrophysiologically compared with 12 consecutive AIDP patients. Cerebrospinal fluid (CSF) interleukin -8 (IL -8) in the acute phase were measured in two patients with A-CIDP and nine with AIDP, was also compared.

Results:
In A-CIDP group, the time from onset to hospitalization was 4 to 12 days (mean 9), and the mean time to first relapse was 87 days (36 to 170). Two patients had dysautonomia, and none had cranial neuropathy and required mechanical ventilation. None had anti-ganglioside antibodies. In AIDP group, the mean age of onset was 51 years, ten patients had cranial nerve damage and five required mechanical ventilation. Initial nerve conduction studies (NCS) in A-CIDP group revealed a sural-sparing pattern (SSP) in one patient, whereas NCS at the time of relapse no SSP. Average CSF IL -8 in AIDP group was higher than in A-CIDP (313.0 v.s. 64.2 pg/ml, $p = 0.059$).

Conclusions:
The absence of cranial nerve damage, no need for mechanical ventilation, and no SSP in the early stage NCS suggest A-CIDP. As shown recently, high levels of CSF IL-8 in acute-phase AIDP may be a promising marker to distinguish between AIDP and A-CIDP.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: acute-onset chronic inflammatory demyelinating polyradiculoneuropathy, acute inflammatory demyelinating poly-neuropathy, Guillain-Barré syndrome, interleukin -8, sural-sparing pattern

Seasonal variational effect of Scrub typhus on Guillain-Barré syndrome in South Korea; retrospective nationwide study

Poster No:
P 487

Authors:
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Introduction:
Scrub typhus is an endemic disease in the Fall season occurred in limited places known as the tsutsugamushi triangle, northern Japan, far eastern Russia, and northern Australia, including South Korea. Guillain-Barré syndrome (GBS) is associated with a previous respiratory or gastrointestinal infection. Thereafter, it occurs more frequently in the Spring and Summer seasons compared to Fall and Winter seasons. Recently we experienced several patients who had ascending paralysis after Scrub typhus infection, finally diagnosed as GBS. So, we consider the seasonal variational effects of Scrub typhus in GBS and its clinical characteristics in South Korea by nationwide study.

Methods:
Patients were retrospectively recruited from 6 nationwide tertiary centers in South Korea from January 2017 to December 2021. We included patients clinically diagnosed with GBS and confirmed infection of Scrub typhus previously by laboratory and/or presence of eschar before the onset of acute limb paralysis. We collected GBS-associated clinical characteristics, electrophysiologic findings, treatment methods, outcomes, and Scrub typhus-associated symptoms and signs of the patients.

Results:
7 patients were enrolled. Six patients were female, and one was male. The median time from Scrub typhus infection to the onset of limb weakness was six days (range, 2-14), and the Medical Research Council sum score of the nadir of patients was 24 (range, 2-40). Four patients were admitted to the intensive care unit and needed artificial ventilator treatment due to respiratory distress. Two patients received a single dose of intravenous immunoglobulin (IVIg), 3 received a second dose of IVIg, and the other 2 received plasmapheresis after IVIg treatment. At six months, the median GBS disability score of the patients was 2 (range, 1-4).

Conclusions:
In this study, we identified clinical characteristics of GBS associated with Scrub typhus. Scrub typhus-associated GBS patients had a more severe clinical presentation and needed intensive treatment with additional immunotherapy.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Guillain-Barré syndrome

The impact of COVID-19 on occurrence and anti-glycolipid antibodies in Guillain-Barré syndrome

Poster No:
P 488

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Institutions:
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Introduction:
Guillain-Barré syndrome (GBS) is an acute immune-mediated neuropathy, approximately 70% of which has antecedent infections. The COVID-19 is an infection caused by the SARS-CoV-2 which has been spreading rapidly. However, the impact of COVID-19 pandemic on GBS is still controversial. We aimed to investigate the changes of occurrence and anti-glycolipid antibodies positivity rates between before and after COVID-19 pandemic.

Methods:
Serum samples from patients with neurological diseases were sent to our laboratory from various hospitals throughout Japan for testing anti-glycolipid antibodies using ELISA. Among them, we extracted 6528 cases suspected of GBS between February 2017 and October 2022. We compared the number of those cases and anti-glycolipid antibody positivity rates between before (2017-2019) and after (2020-2022) COVID-19 pandemic.

Results:
The number of the cases were 3889 before pandemic and 2639 after pandemic. Average number of cases per month was 108 before pandemic, and 78 after pandemic. The positive ratio of IgG antibodies was 44% vs 45% ($p > 0.05$). Positive rate of anti-GD1b and -GQ1b IgG antibodies were significantly decreased from 15% to 12 % and from 9% to 5% ($p < 0.01$, respectively), while those of anti-GM1 antibodies were significantly increased from 18% to 29% ($p < 0.01$).

Conclusions:
The number of patients suspected of GBS possibly decreased after COVID-19 pandemic. Prevention of the spread of COVID-19 could influence the positivity rate of each anti-glycolipid antibody.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Guillain-Barré syndrome, COVID-19, anti-glycolipid antibody

Magnetic Resonance Neurography at the Site of Conduction Block in Multifocal Motor Neuropathy

Poster No:
P 489

Authors:
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Institutions:
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Introduction:
Multifocal motor neuropathy with conduction block (MMNCB or MMN) is an inflammatory neuropathy characterized by progressive, asymmetric and predominantly upper limb weakness without sensory involvement. The diagnosis is based on clinical multiple motor mononeuropathies and persistent neurophysiological motor conduction block. The clinical features can mimic motor neurone disease (MND) and when conduction block cannot be demonstrated neurophysiologically, it can be difficult to differentiate MMNCB from MND. Conduction block can often be localised quite accurately in the forearm by 'inching'.

Methods:
Using 3T magnetic resonance (MR) neurography, we explored if there was any identifiable and diagnostic MRI characteristic at the site of conduction block. All patients underwent neurophysiology studies to define sites of forearm conduction block. All subjects underwent 3.0 Tesla MRI scans of both forearms. We acquired T1-weighted images of the forearm (T1 Vibe Dixon), T2-STIR-weighted and T2-weighted structural scans, followed by axial DTI scans. Regions of interest were drawn on the raw diffusion data in the proximal, middle and distal third of each of the three forearm nerves and used to seed the tractography in MRtrix3. This allowed us to visualize the nerves and extract diffusion parameters for comparison between patients and controls and within-disease comparison between the forearm with block and the forearm without block.

Results:
We enrolled ten MMN patients and ten age and gender-matched healthy controls. The average age was 46.2 ± 15.7 years for patients and 48 ± 12 years for controls. Only one patient had definite conduction block in both arms. Six patients had conduction block in one nerve only. One patient had definite conduction block in all three nerves of the right forearm and two patients had one definite conduction block and another probable conduction block in the same arm.

Conclusions:
All data have been acquired and results will be presented.

References:
Yes

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J.-D. Tournier, R. E. Smith, D. Raffelt, R. Tabbara, T. Dhollander, M. Pietsch, D. Christiaens, B. Jeurissen, C.-H. Yeh, and A. Connelly. MRtrix3: A fast, flexible and open software framework for medical image processing and visualisation. NeuroImage, 202

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Grant Support: Muscular Dystrophy UK GAIN Charity (GBS and Associated Inflammatory Neuropathies), UK

Keywords: multifocal motor neuropathy, MR neurography, conduction block

Guillain–Barré Syndrome in Northern China: A Retrospective Analysis of 294 Patients from 2015 to 2020

Poster No:
P 490

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Introduction:
Acute motor axonal neuropathy (AMAN) was first reported to be the main subtype of Guillain–Barré syndrome (GBS) in northern China in the 1990s. About 30 years has passed, and it is unknown whether the disease spectrum has changed over time in northern China.We aimed to study the epidemiological, clinical, and electrophysiological features of GBS in northern China in recent years.

Methods:
We retrospectively analyzed the medical records of GBS patients admitted to our hospital in northern China from 2015 to 2020.

Results:
A total of 294 patients with GBS were enrolled, with median age 53 years and 60.5% of participants being male, and a high incidence in summer and autumn. AMAN was still the predominant subtype in northern China (40.1%). The AMAN patients had shorter time to nadir, longer hospitalization time, and a more severe HFGS score at discharge than acute inflammatory demyelinating polyneuropathies (AIDP) ($p < 0.05$). With SPSS multivariable logistic regression analysis, we found the GBS disability score (at admission), dysphagia, and dysautonomia were independent risk factors for GBS patients requiring MV ($p < 0.05$). In comparison with other regions, the proportion of AMAN in northern China (40.1%) was higher than in eastern (35%) and southern (19%) China

Conclusions:
AMAN is still the predominant subtype in northern China after 30 years, but there have been changes over time in the GBS spectrum since the 1990s. There are regional differences in GBS in China.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: This work was supported by the Health Commission of Hebei Province (grant number 20200889).

Keywords: Guillain–Barré Syndrome, Retrospective Analysis , Northern China

Impact of Gut Microbiota on Nerve Repair Following Traumatic Peripheral Nerve Injury

Poster No:
P 491

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Introduction:
Combat and civilian trauma to limbs often results in serious injuries to the peripheral nerves that cause significant morbidity. Surgical repair is still the first line of treatment for many of the traumatic peripheral nerve injury (PNI). However, current therapeutic options do not achieve good motor and sensory nerve function recovery in all cases, especially in elderly patients. The inflammatory response in the distal nerve stump is pivotal to nerve repair after PNI. Studies have shown that the age-dependent decline in regenerative capacity of peripheral nerves is associated with elevated chronic inflammation. Therefore, discovering therapeutic strategies that modulate immune cells in a way that reduces tissue damage and promotes axon growth would be highly desirable. Enhanced age-related inflammation has been linked to gut microbiota imbalance. The gut microbiome is a balanced ecosystem which plays a major role in maintaining gut-immune equilibrium. Under certain circumstances the balance of the microbiome is disrupted leading to chronic inflammation and alterations in immunity. Thus, understanding the influence of commensal gut microbiota in PNI represents a novel area of medical research.

Methods:
This work examined whether manipulation of gut microbiome to reverse gut microbial dysbiosis influences systemic and endoneurial inflammatory state of host, and further determined whether microbiome restoration therapy using a probiotics cocktail can improve neurological recovery in peripheral nerve injury models, including a standardized sciatic nerve crush model and sciatic nerve transection model.

Results:
We found that aging causes significant shifts in gut microbiota and microbial metabolites. Furthermore, restoration of a healthy microbiome by fecal transplant to aged mice enhances nerve function recovery after PNI.

Conclusions:
It is both conceivable and practical that patients with traumatic nerve injuries undergoing elective repairs be tested for gut dysbiosis and those with dysbiosis could undergo microbiome restoration with probiotics, a readily available translationally relevant approach.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Traumatic peripheral nerve injury, Microbiome, Aging, Microbial dysbiosis, Inflammation

Efficacy of hematopoietic stem cell transplantation treatment in refractory chronic inflammatory demyelinating polyradiculoneuropathy: a systematic re

Poster No:
P 492

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Introduction:
Treatment options for Chronic inflammatory demyelinating polyneuropathy (CIDP) are intravenous immunoglobulin (IVIg), plasmapheresis (PE), corticosteroids and immunosuppressive drugs. However, a substantial proportion of patients with CIDP remain refractory to treatment and had severe functional disability. We performed a systematic review and a meta-analysis of the efficacy of hematopoietic stem cell transplantation (HSCT) treatment in refractory CIDP patients.

Methods:
Through searches in PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE, Web of science and clinicaltrials.gov databases on 4 December 2022. Papers met our eligibility criteria were included after screen. Patients' characteristics, treatment regime and outcome measure were extracted.

Results:
Eighty-nine patients in 11 studies were included. The pooled estimate of responsiveness among the four included studies was 87.04% (95% CI 66.7–99.5%) and the pooled estimate of freedom of all immune modulating or suppressive drugs was 80.75% (95% CI 71.2–90.2%).

Conclusions:
This meta-analysis and systematic review suggest that HSCT can be effective in the treatment of refractory CIDP. While there are risks involved, HSCT may be a beneficial and viable therapy for refractory CIDP when carefully evaluated.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Chronic inflammatory demyelinating polyneuropathy , hematopoietic stem cell transplantation, Treatment

Anti-NF 186 antibody positive combined central and peripheral demyelination: A case report

Poster No:
P 493

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Introduction:
NF186 are present both in central nervous system (CNS) and peripheral nervous system (PNS). So far, no NF186 antibody positive CCPD case has been reported.

Methods:
A 37 years old Chinese woman, developed weakness in the lower limbs and walking unsteadiness. On neurological examination, power was 5 of 5 in upper limbs and 4 of 5 in lower limbs. All tendon reflexes were +1, except bilateral ankle reflexes were +3, without positive Babinski sign. Vibration and pin sensation were normal on both sides. Dysmetria was noted bilaterally on the finger-to-nose and heel-to-shin tests. Truncal ataxia was noted. Biochemical test ,immunofixed electrophoresis and paraneoplastic antibodies were negative. Cerebrospinal fluid examination showed elevation of protein (725mg/dl). Second generation sequencing were negative. Brain MRI showed symmetry T2 high signal intensities involving bilateral ovoid lesions. She did serum test for anti NF186 antibody by Cell Based Assay showed positive :(1:100). The type of IgG was IgG 3

Results:
NCS revealed reduced amplitudes of CMAP and SNAP in upper and lower limb nerves. EMG showed denervation potential in four limbs. After that the patient received treatment with methylprednisolone, PE and Rituximab for two months. Unsteadiness gradually relieved and muscle strength of lower limbs was improved,as well as nomadized EMG and brain MRI.

Conclusions:
Our case had different clinical characteristic compare with NF 155 antibody positive CCPD, onset age was older, subacute onset with polyneuropathy, recover soon after steroid treatment, root hypertrophy is not observed; However, brain lesion and cerebellar sign was prominent, partially responded to steroid but relapse over times, PE and Rituximab may be more efficient for CNS lesion. The case also presented with reversible conduction failure, which is a sign of nodopathy ,related with anti-NF186 antibody which is crucial for the cluster of sodium channel in the nodes of Ranvier.

References:
Yes

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Kawamura N, Yamasaki R, Yonekawa T et al (2013) Antineurofascin antibody in patients with combined central and peripheral demyelination. Mult Scler J 19(11):88

References 2:

References 3:

References 4:

Grant Support:

Keywords: nf186, ccpd

Electrophysiology and imaging characteristics of chronic inflammatory demyelinating neuropathy

Poster No:
P 494

Authors:
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Introduction:
Classic CIDP, Lewis-Sumner syndrome (LSS)and Multifocal Motor Neuropathy (MMN) have similar clinical manifestations but different treatment options and prognosis. We analysis the electrophysiology and brachial plexus MRI characteristics of these three types of chronic inflammatory neuropathy to better classification and treatment.

Methods:
In retrospective analysis, 9 LSS (109 nerves), 9 MMN (109 nerves) and 10 classic CIDP (89 nerves) were involved. Clinical data were collected. Electrophysiology data include motor nerve studies in the median, ulnar, tibial and sensory nerve studies in median, ulnar and sural nerves. Distal motor latency, amplitudes of CMAP and SNAP, NCV, conduction block and F wave latencies were recorded.MRI of the brachial plexus were also collected.

Results:
The classic CIDP showed prolonged DML, slowed MCV, prolonged or absent F wave latency, more severe than LSS and MMN, indicating more extensive demyelination in proximal and distal part of peripheral nerves. The distribution of these abnormal were symmetrically. MMN and LSS presented more conduction block than classic CIDP. In MMN and LSS the most common part to find CB is forearm of median nerve and upper arm of ulnar nerve. The reduction of CMAP amplitudes and abnormal EMG findings in classic CIDP were significantly more severe than LSS and MMN, which means axonal loss secondary to diffuse demyelinating changes. For sensory nerve studies, MMN didn't present any abnormalities, but LSS and Classical CIDP showed median and ulnar nerve were more severe involved than sural nerves. As for brachial MRI, classic CIDP was with the highest abnormal rate (100%), while the abnormal rate of LSS is 60% and MMN was 66%.

Conclusions:
Classic CIDP, LSS and MMN presented different distribution of segmental demyelination in median and ulnar nerve motor studies which can help distinguish these three types. MRI of brachial plexus is valuable in the diagnosis of CIDP.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: cidp, lss, mmn

Sulforaphane promotes repair Schwann cell function via Nrf2/HO-1 signaling

Poster No:
P 495

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Introduction:
Nuclear erythroid 2–related factor 2 (Nrf2) is commonly activated in response to cellular stresses such as oxidative damage and drives expression of various factors involved in cytoprotection and dampening of inflammatory processes. The activation of the Nrf2/HO-1 signaling pathway has been associated with markedly accelerated peripheral nerve regeneration by clinical, electrophysiological as well as histological measures. However, the exact mechanisms underlying these improvements have not been elucidated so far. To better understand the role of Nrf2 following peripheral nerve injury, we aimed to study the consequences of treatment with the Nrf2 activator sulforaphane (SFN), a naturally occurring isothiocyanate from cruciferous plants, in the murine sciatic nerve crush model.

Methods:
SFN was administered daily via intraperitoneal injection at a dose of 10 mg/kg, starting immediately after sciatic nerve crush injury was introduced. Animals were sacrificed and sciatic nerves were excised at 7, 14 and 21 days post-crush (dpc) for molecular, immunohistochemical and morphometric analyses. Moreover, clinical testing by grip strength analysis and electrophysiology was performed.

Results:
From the end of Wallerian degeneration at 7 dpc, we noted a marked upregulation of the Nrf2/HO-1 signaling pathway under treatment with SFN, which was maintained throughout the entire regeneration phase until 21 dpc. This effect was accompanied by a significant increase in the number of repair Schwann cells as identified by positivity for Sox-2, c-Jun and p75-NTR. In these cells, we also observed elevated proliferation rates identified by Ki67 staining. Concomitantly, apoptotic/autophagic pathways were modulated. These observed changes correlated with a significant clinical improvement in the grip strength test performance, nerve conduction velocity as well as ameliorated histopathological measures at 21 dpc.

Conclusions:
Collectively, SFN treatment was associated with an upregulation of cytoprotective pathways, leading to increased numbers of repair Schwann cells that presumably contribute to a permissive environment for successful nerve regeneration.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Repair Schwann Cell, Nerve crush, Nerve Regeneration

Porous Nanoparticle Incorporated Scaffolds for Release of Active Neurotrophic Payloads

Poster No:
P 496

Authors:
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Institutions:
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Introduction:
Nerve guidance conduits are studied extensively in efforts to replace, enhance, or reduce the use of nerve autograft treatments following peripheral nerve injury. However, conduits still inadequately promote nerve regeneration after injury, and are seldom used in the clinic. In order to improve guidance conduits, neurotrophic payloads have begun to be incorporated into scaffolds. Here, we demonstrate the ability of porous silicon nanoparticles to load, protect, and release three different classes of active neurotrophic payloads, small molecule, protein, and nucleic acid, from polymer nanofiber scaffolds to enhance neurite extension.

Methods:
Porous silicon nanoparticles were created via electrochemical etching of highly boron doped p-type silicon wafers. bpV(HOpic) was then loaded with an adsorption technique, nerve growth factor was loaded by oxidation trapping, and TrkB aptamers were loaded with calcium silicate trapping. Nanoparticles were incorporated into nanofiber scaffolds using an airbrush fabrication technique. Material properties and payload release were determined using electron microscopy, atomic force microscopy, and spectroscopy. Dorsal root ganglia were isolated from post-natal day 2 C57BL/6J mouse pups, seeded onto nanofiber scaffolds, and cultured for 7 days. DRG were then fixed, stained (anti-Neurofilament-200, Hoechst 33342), and imaged to quantify neurite extension and cellular migration.

Results:
Nanoparticle incorporated scaffolds released bpV(HOpic) over a 10 day period, TrkB aptamers over a 20 day period, and NGF over a 40 day period. DRG cultured on the aligned nanofiber scaffolds demonstrated significantly longer neurite extension on scaffolds releasing bpV(HOpic), TrkB aptamers, or nerve growth factor compared to control scaffolds without payload nanoparticles.

Conclusions:
Porous nanoparticles can load, protect, and modify the release of sensitive neurotrophic payloads. When incorporated into aligned nanofiber scaffolds, DRG neurite extension is directed by the nanofiber topography and enhanced by the release of the neurotrophic payloads. This demonstrates the efficacy of using nanoparticle payload release for nervous system repair.

References:
No

References 1:

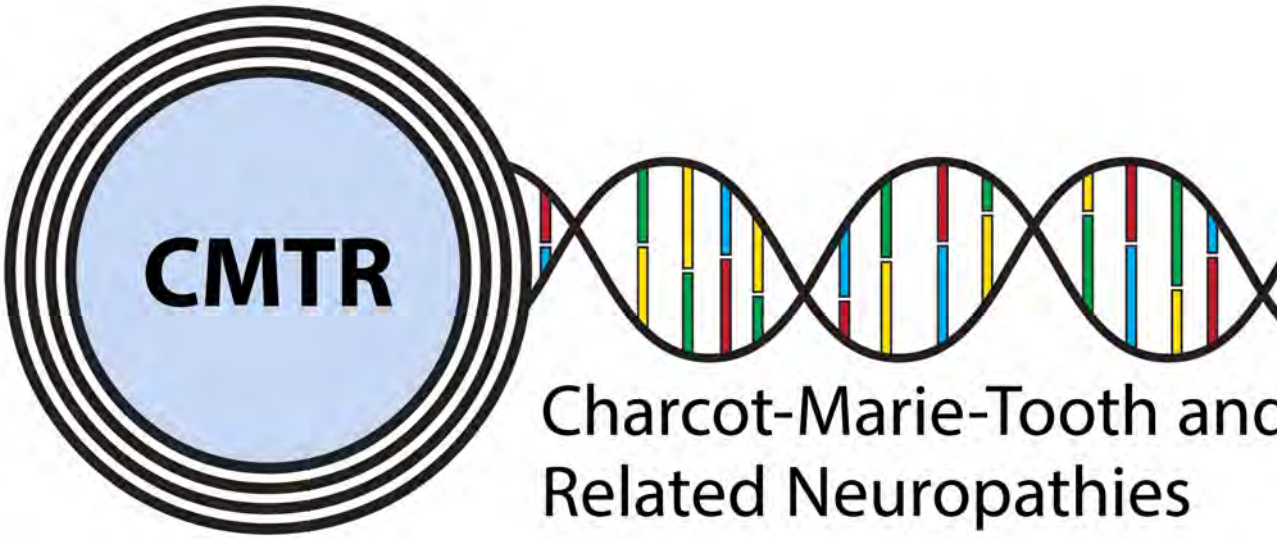
References 2:

References 3:

References 4:

Grant Support: National Science Foundation under Grant No. CBET-1603177 (M.J.S.), and in vitro DRG studies were supported in part by the National Institutes of Health under Grant No. NIBIB-RO1-EB005678. JMZ is a MSCA Fellow, agreement No. 1016770 (“PACMAN”).

Keywords: Neurotrophic Factor Delivery, Dorsal Root Ganglia, Nerve Guidance Scaffold, Neurite Extension, Nanomedicine



Charcot-Marie-Tooth and Related Neuropathies (CMTR) Abstracts

O 497 - 519

Novel pathogenic repeat configurations in RFC1 causing CANVAS and disease spectrum

Poster No:
O 497

Authors:
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Introduction:
Cerebellar Ataxia, Neuropathy and Vestibular Areflexia Syndrome (CANVAS) is an autosomal recessive ataxia, usually caused by biallelic (AAGGG)n repeat expansions in RFC1. However, a minority of CANVAS patients do not carry AAGGG repeat expansions. We identified three novel repeat motifs associated with CANVAS and we demonstrated a pathogenic role for large AAAGG repeat expansions.

Methods:
We analysed 893 short-read-WGS from adult patients with ataxia diagnosis and 8107 controls from the 100000GenomeProjects, and detected repeat expansions at the RFC1 locus using ExpansionHunterDeNovov0.9.0. Repeat motifs in homozygosis or compound heterozygosis with AAGGG in patients and absent in controls were further investigated by long read sequencing. Compound heterozygous AAAGG/AAGGG carriers were also further studied, given their higher frequency in ataxia cases.

Results:
We identified six CANVAS patients carrying novel repeat expansions in RFC1, namely (AGGGC)n (n=3), (AAGGC)n (n=2), (AGAGG)n (n=1), which were absent in controls. Repeat size was >500 repeat units in all cases and up to 3400 in AGGGC repeat expansion carriers. Long-read-sequencing revealed a pure AGGGC expansion in three patients, whereas the other patients presented complex motifs with AAGGG or AAAGG interruptions. These configurations seem to have arisen from a common haplotype. We also identified four CANVAS patients carrying uninterrupted or interrupted AAAGG repeats. Pathogenic AAAGG expansions were >600 units (mean±SD, 892±247), and were significantly larger

compared to non-pathogenic AAAGG expansions (173±232). Clinical features of patients with novel repeat configurations were mostly indistinguishable from biallelic AAGGG repeat expansions carriers.

Conclusions:
The identification of novel pathogenic configurations and the demonstration of a pathogenic role for the AAAGG repeat expands the genetic heterogeneity of RFC1 disease. The assessment of these novel configurations is warranted in CANVAS patients with inconclusive genetic testing. Particular attention should be paid to carriers of compound AAGGG/AAAGG expansions and sizing and full sequencing of the satellite through long read is recommended.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: CANVAS, RFC1, Long read sequencing, Repeat expansion disorders, Sensory neuropathy

Deficiency of ADA2 (DADA2) syndrome: A case series

Poster No:
O 498

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Introduction:
Deficiency of ADA2 (DADA2) syndrome is an autosomal recessive monogenic vasculitis syndrome caused by mutation in the ADA2 gene. It affects multiple organs including skin, central nervous system, peripheral nervous system, haematological and gastrointestinal systems. In this case series, we aim to describe three cases of a rare genetic neuropathy, (DADA2) syndrome.

Methods:
We included all clinically suspected cases of DADA2 diagnosed in the comprehensive neuromuscular disorders clinic in our centre. Diagnosis was based on involvement of two or more of the following: peripheral neuropathy, necrotising vasculitis in medium vessels, brain imaging showing stroke or aneurysm, immune dysfunction, bone marrow dysfunction, testicular pain, cutaneous involvement, hypertension, renal involvement (proteinuria, hematuria) and gastrointestinal involvement. All patients underwent deep phenotyping and nerve conduction studies (NCS), blood investigations for vasculitis, viral markers and angiography. One patient underwent skin biopsy. Two patients underwent singleton clinical exome sequencing and one patient underwent singleton whole exome sequencing (WES) in the MRC-funded International Centre for Genomic Medicine in Neuromuscular Diseases (ICGNMD) study.

Results:
Five patients were clinically suspected of DADA2 and after exome sequencing, 3 patients were solved involving ADA2 gene. Other two patients were treated as systemic vasculitis. Among the three solved cases, the median age of onset was 28 years (range 25-42) and all were males. All had brain involvement (stroke, seizures or cognitive involvement). Two patients had peripheral neuropathy. Skin, gastrointestinal, constitutional hypertension were present in all patients. Two patients had visceral infarcts and vascular aneurysms. As for management, one patient received etanercept after genetic diagnosis and two patients received multiple immunosuppressants including corticosteroids, azathioprine, mycophenolate mofetil, IVIG and Rituximab. After genetic confirmation, one patient received adalimumab. Other patient continued on Azathioprine. One patient died after surgery for intestinal perforation.

Conclusions:
DADA2 should be considered in patients with childhood polyarteritis nodosa like presentation and young onset multisystem vasculitis.

References:
No

References 1:

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References 3:

References 4:

Grant Support: Medical Research Council (UK) strategic award to establish an International Centre for Genomic Medicine in Neuromuscular Diseases (MR/S005021/1).

Keywords: DADA, vasculitis, monogenic vasculitis

Homozygous *NDUFS6* Splice Variant Highlights The Importance Of Peripheral Neuropathy In The Clinical Spectrum Of Primary Mitochondrial Disorders

Poster No:
O 499

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Introduction:
NDUFS6 is a nuclear mitochondrial gene that encodes a subunit of Complex I (CI). Biallelic mutations in this gene have been associated with fatal infantile CI deficiency[1,2,3]. Until now, all the cases reported in the literature do not live beyond the first year of life. The aim of this presentation is to report 5 patients from 3 unrelated families with axonal Charcot-Marie-Tooth (CMT) neuropathy harboring a homozygous splice variant in *NDUFS6* .

Methods:
Whole exome sequencing was performed in two siblings with a diagnosis of axonal autosomal recessive CMT. After exclusion of mutations in known CMT genes, variant filtering and prioritization within regions of homozygosity was conducted. The functional effect of the resulting variant was characterized in patient-derived EBV-transformed lymphoblasts at the RNA, protein and mitochondrial level. Screening of additional families with variants in the gene was performed on an in-house cohort and in external databases.

Results:
We have found a homozygous splice-site variant c.309+5G>A in *NDUFS6* in 5 patients (2 adults and 3 adolescents) with slowly progressive axonal ARCMT and nystagmus. The splice variant leads to expression of multiple aberrantly spliced transcripts and negligible levels of canonical transcript. Immunoblotting showed the presence of at least 2 mutant isoforms but overall shows reduced levels of NDUFS6 protein. In contrast to the fatal cases reported in the literature, the milder phenotype of these patients could be attributed to the aberrantly spliced isoforms which preserve the last cysteine of the Zinc-finger domain. This residue has been reported to be essential for CI assembly and stability[4].

Conclusions:
This work provides evidence to support that *NDUFS6* is a novel disease-causing gene for CMT, expanding the clinical spectrum of *NDUFS6*-related mitochondrial disorders. Our findings stress the importance of splicing as it might differentiate between a lethal and viable phenotype.

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Yes

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Grant Support:

Keywords: CMT, Mitochondria, Splicing

Imbalance of NRG1 type III-ERBB2/3 signaling underlies altered myelination in Charcot-Marie-Tooth disease type 4H

Poster No:
O 500

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Introduction:
Charcot Marie Tooth (CMT) disease is a heterogeneous group of inherited neuropathies, affecting either axons from the motor and sensory neurons (axonal form) or Schwann cells (demyelinating form). We previously identified mutations in FGD4 encoding FRABIN, a GDP/GTP nucleotide exchange factor, as responsible for CMT4H. CMT4H is an autosomal recessive demyelinating form of CMT displaying excessive myelin loops called outfoldings. Those abnormalities arising from focal hypermyelination suggest that FRABIN could play a role in the control of peripheral nervous system (PNS) myelination.

Methods:
To gain insights into the role of FGD4/FRABIN in PNS myelination, we generated a knock-out mouse model (Fgd4SC-/-), with conditional ablation of Fgd4 in Schwann cells. In particular, we used an in vitro myelin model derived from these mice (dorsal root ganglia neurons/ Schwann cells cocultures) combined to transcriptomic and yeast two-hybrid screen studies to reveal new molecular actors in CMT4H pathology.

Results:
We showed that Fgd4SC-/-cocultures as well as distal sciatic nerves display aberrant myelination defects. We demonstrated that those abnormalities are related to an upregulation of some actors of the NRG1 type III/ERBB2/3 signaling pathway. Based on a yeast two- hybrid screen, we identified SNX3 as a new partner of FRABIN, which is involved in the regulation of endocytic trafficking. Using RNA-Seq in vitro, we revealed new effectors of the deregulated pathways, such as ERBIN, RAB11FIP2 and MAF, which may contribute to proper ERBB2 trafficking or even myelin membrane addition, through cholesterol synthesis. Finally, we demonstrated that the reestablishment of proper levels of the NRG1 type III/ERBB2/3 pathway, using Niacin treatment, restores proper myelination in nerves of CMT4H mice.

Conclusions:
Our work demonstrates a new role of FRABIN in the regulation of NRG1 type III/ERBB2/3 signaling pathway and PNS myelination. These findings open future therapeutic strategies, based on the modulation of the NRG1 type III/ERBB2/3 pathway, to reduce CMT4H pathology.

References:
No

References 1:

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Grant Support:

Keywords: Charcot-marie-tooth, myelin outfoldings, endocytic trafficking, NRG1/ERBB2/3, Niacin

Mutations in MYO9B are associated with CMT2 neuropathies and isolated optic atrophy

Poster No:
O 501

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Introduction:
Charcot-Marie-Tooth disease (CMT) is a heterogeneous group of inherited neuropathies generally characterized by distal motor and/or sensory deficits that progress with age. Since the advent of next generation sequencing (NGS), the number of novel genes and causative variants identified as responsible for CMTs has dramatically increased. However, approximately 60% of cases of the axonal forms (including CMT2, HMN, and HSAN) remain genetically undiagnosed, due, in part, by a large number of unknown rare genetic causes. We aimed at identifying novel disease genes responsible for CMT2.

Methods:
We performed WES and targeted NGS panel analyses on a cohort of CMT2 families with evidence for autosomal recessive inheritance. We also performed functional studies to explore the pathogenetic role of selected variants.

Results:
We identified rare, recessive variants in the MYO9B (Myosin IX) gene in two families with CMT2. MYO9B has not been yet associated with a human disease. MYO9B is an unconventional single-headed processive myosin motor protein with signaling properties, and, consistent with this, our results indicate that a variant occurring in the MYO9B motor domain impairs protein expression level and motor activity. Interestingly, a Myo9b-null mouse has degenerating axons in their sciatic nerves and optic nerves, indicating that MYO9B plays an essential role in both PNS and CNS axons, respectively. The degeneration observed in the optic nerve prompted us to screen for MYO9B mutations a cohort of patients with optic atrophy (OA). Consistent with this, we found compound heterozygous variants in one case with isolated OA.

Conclusions:
Here we report that novel or very rare variants in MYO9B are associated with CMT2 and OA

References:
Yes

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Cipriani et al., Eur J Neurol. 2023 Feb;30(2):511-526.

References 2:

References 3:

References 4:

Grant Support:

Keywords: Charcot-Marie-Tooth, Myosin

Validation of the CMT Functional Outcome Measure (CMT-FOM)

Poster No:
O 502

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Introduction:
For patients with CMT1A, few clinical trials have been performed, however multiple therapies have reached an advanced stage of pre-clinical development. A well-validated Clinical Outcome Assessment (COA) in accordance with the FDA qualification program of how adults with CMT function is needed for upcoming disease-modifying trials.

Methods:
214 patients aged 18 to 75 years with CMT1A (58% female) were recruited through CMT clinics in the USA (n=130), United Kingdom (n=52) and Italy (n=32) as part of the Accelerate Clinical Trials in Charcot-Marie-Tooth disease (ACT-CMT) Project. A series of validation studies were conducted, including item and factor analysis, Rasch model analysis, and testing of inter-rater reliability, discriminative ability and convergent validity.

Results:
A psychometrically robust 12-item scale was constructed, the CMT-FOM, covering upper and lower limb strength, hand dexterity, lower extremity function, balance and mobility. Rasch analysis supported the viability of the CMT-FOM as a unidimensional interval scale of function in adults with CMT1A. The CMT-FOM ranges from 0 (indicating no impairment) to 100 (indicating severe impairment) and showed good overall model fit, no evidence of misfitting items, and no person misfit, and it was well targeted for adults with CMT1A.

Conclusions:
The Rasch-derived 12-item CMT-FOM is a unidimensional performance-based COA reflecting how patients with CMT1A function. The CMT-FOM is a multi-item, disease-specific, psychometrically robust COA addressing the FDA guidance that function is a key clinical endpoint to identify therapeutic efficacy.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: Accelerate Clinical Trials in Charcot-Marie-Tooth disease (ACT-CMT) project (NIH #NINDS 1U01NS109403)

Keywords: clinical outcome assessment, Charcot-Marie-Tooth disease type 1A, performance outcome measure, clinical trials

Novel HDAC6 inhibitor AGT-216 halts CMT1A disease progression in symptomatic mice

Poster No:
O 503

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Introduction:
Charcot-Marie-Tooth disease (CMT) is a debilitating disorder affecting the peripheral nervous system. The most common form, CMT1A, is caused by a duplication of the PMP22 gene. For the past decade, histone deacetylase 6 inhibitors (HDAC6i) have been intensively investigated in several forms of CMT and have shown therapeutic effects which correlated with their ability to restore axonal transport deficits and to reinnervate neuromuscular junctions. A recent high-throughput-screen has led to the identification of a novel class of non-hydroxamic acid and non-oxadiazole selective HDAC6i, and ultimately to AGT-216 lead candidate

Methods:
In vitro pharmacology of AGT-216 was investigated in biochemical and cellular assays. AGT-216 efficacy was evaluated using the CMT1A C3 mouse model with 5 copies of the human PMP22 gene integrated in their genome. Symptomatic C3 mice (8 weeks of age) were administered AGT-216 daily via oral gavage. Behavioral and electrophysiological measurements were performed at 10 and 12 weeks of age. Plasma and sciatic nerves were isolated for biomarker and histological (semi-thin) analysis.

Results:
AGT-216 displayed high inhibitory potency versus both full length HDAC6 protein and HDAC6-CD2 domain. Grip strength analysis demonstrated that AGT-216 treated C3 mice had a significant improvement. Compound muscle action potentials and nerve conduction velocities were significantly improved by AGT-216 treatment in comparison to the C3 control mice. Moreover, acetylated α-tubulin was significantly reduced in sciatic nerve of the C3 mice and this was significantly increased by AGT-216. Neurofilament light chain was highly elevated in plasma and sciatic nerve of the C3 mice and was significantly decreased in AGT-216 treated mice. Lastly, semi-thin analysis demonstrated improved axonal diameters and myelin g-ratios in AGT-216 treated C3 mice.

Conclusions:
Our data demonstrate that the selective, non-hydroxamate and non-oxadiazole HDAC6i, AGT-216, halts the disease and reverses the pathological hallmarks of the disease in symptomatic CMT1A mice.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: FLANDERS INNOVATION & ENTREPRENEURSHIP (VLAIO)

Keywords: Charcot-Marie-Tooth disease, CMT1A, non-hydroxamic acid HDAC6 inhibitor, AGT-216, C3 mice

Repairing dominant genetic forms of CMT and ALS/FTD with allele-specific CRISPR editing

Poster No:
O 504

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Introduction:
We are using human iPSC disease models to discover optimal methods to selectively inactivate disease genes by allele-specific CRISPR genome editing. This strategy is particularly promising for diseases involving haplosufficient genes where mutations are inherited in a dominant fashion and the remaining normal allele is sufficient to maintain health of the cell. This class of genetic disease is particularly common in neurodegeneration. A majority of the >100 Charcot-Marie-Tooth (CMT) disease genes may be 'dominant-haplosufficient' and could benefit from this therapeutic approach.

Methods:
We are focusing on multiple genes implicated in CMT (MFN2, NEFL) and ALS (FUS) to establish best practices that will enable us to expand this method to additional genes (e.g. GARS, HSPB1, PMP22, MPZ). Selective editing of the disease allele in vivo requires 4 major advances: 1. Delivering CRISPR reagents. We are using iPSC-neurons and animal models to test viral-like particles and lipid nanoparticles. 2. Controlling DNA damage repair in neurons. We have found that the DNA repair machinery in neurons can be altered to change editing outcomes in a manner that could enhance precise editing.

Results:
3. Utilizing common SNPs to enable a small number of allele-specific edits to treat many ultra-rare disease mutations. Many disease mutations are ultra-rare and require different CRISPR reagents for each patient using previous methods. In contrast, we target CRISPR to selectively inactivate major haplotypes for each gene so that the majority patients could be treated with just 4 to 6 CRISPR guides. 4. Understanding the role of epigenetics in CRISPR editing. We are developing high-throughput methods to interrogate single and dual guide editing at endogenous loci. This will allow us to infer how 3D genome structure and gene expression affect CRISPR editing.

Conclusions:
These rules will help us predict the ideal methods for allele-specific editing in many other gene targets.

References:
No

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References 2:

References 3:

References 4:

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Keywords: CRISPR, induced pluripotent stem cells, DNA damage repair, CMT, ALS

Biallelic variants in ARHGAP19 cause mixed demyelinating and axonal polyneuropathy

Poster No:
O 505

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Introduction:
Rho GTPases are members of the large superfamily of small GTPase proteins considered as molecular switches in various cellular events. One of the major regulators of Rho-GTPases are Rho-GTPase-activating proteins (GAPs). RhoGAPs stimulate intrinsic GTPase activity of Rho-GTPases therefore acting as negative regulators of Rho pathway. One of the Rho effectors, the serine/threonine protein

kinase ROCK, has important role in actin organisation, cell migration regulation, cell cycle control, and cell adhesion.

Methods:
We are using various approaches to model these variants; in-vitro GAP assays to assess if the GAP activity is affected by expression of proteins carrying ARHGAP19 mutations, complemented by an in-vivo Drosophila melanogaster model to test movement, lifespan and neuromuscular junction integrity; in-silico approach to gain an understanding of protein structure changes and its implications.

Results:
By using next-generation sequencing we identified 16 individuals from 14 unrelated families with biallelic variants in ARHGAP19, presenting with young age of onset progressive weakness in lower limbs, difficulty in walking and foot deformities. Nerve conduction studies reveal mixed demyelinating and axonal polyneuropathy. Ongoing studies such as the in-vitro GAP assays show that ARHGAP19 has GAP activity towards RhoA but not Rac1 or Cdc42. Three of the mutations found in patients are being tested for their GAP activity and preliminary data suggest a loss of the GAP activity in a frame shift mutation. Visualisation of the endogenous expression pattern of ARHGAP19 ortholog in fly, RhoGAP54D, suggest the protein is expressed in perineural or subperineural glia in the fly brain. Preliminary results indicate that RNAi knockdown of RhoGAP54D in flies reduces both overall movement and startle responses to light-dark transitions.

Conclusions:
This is a first association of ARHGAP19 with neurological disease and deep phenotyping analysis in conjunction with the in-vivo animal model and in-vitro GAP assay will help highlight the importance of the gene in early human brain development and function.

References:
No

References 1:

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References 3:

References 4:

Grant Support:

Keywords: ARHGAP19, NGS, GAP assay, fruitfly, gene discovery

Fatty-Acid–Conjugated PMP22 siRNA Reverses Charcot-Marie-Tooth Type 1A Features in a CMT1A Mouse Model

Poster No:
O 506

Authors:
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Introduction:
Charcot-Marie-Tooth 1A Disease (CMT1A) affects 150,000 patients in the U.S. and Europe and is caused by a duplication of the gene for peripheral myelin protein 22 (PMP22), a glycoprotein expressed in Schwann cells. PMP22 duplication leads to defective myelination of peripheral nerves causing nerve dysfunction, which leads to muscle atrophy and weakness, difficulty walking, and abnormal hand function. There are no approved treatments for CMT1A. We used our Fatty-Acid–Ligand-Conjugated OligoNucleotide platform, which we call FALCON, to deliver siRNAs to Schwann cells in the peripheral nervous system for the potential treatment of CMT1A.

Methods:
We tested our FALCON siRNA targeting human PMP22 (hPMP22), DTx-1252, in a transgenic CMT1A (C3) mouse model that has been genetically modified to express 3–4 copies of the hPMP22 gene and closely mimics the pathophysiology of CMT1A in humans. DTx-1252 was administered intravenously to C3 mice every 4 weeks for a total of 12 weeks. Throughout the study electrophysiological endpoints (motor-nerve–conduction velocity (MNCV) and compound muscle action potentials (CMAP) were measured. At week 12, nerve samples were harvested and hPMP22 as well as other disease relevant genes were analyzed.

Results:
DTx-1252 treatment reduced hPMP22 mRNA levels in peripheral nerves up to 90%, leading to remyelination of peripheral nerves; improvement in MNCV and CMAP; and improved motor coordination (beam walking), grip strength, and muscle mass up to WT levels. We observed a dose-proportional response and increased effects of hPMP22 knockdown following multiple doses. At week 12, DTx-1252 treatment also decreased the expression of peripheral nerve genes that were dysregulated in C3 mice relative to WT mice.

Conclusions:
These results showed that DTx-1252 significantly decreased hPMP22 expression and ameliorated disease features in the C3 mouse model. They support the use of DTx-1252 as a potential treatment for CMT1A in patients.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: CMT1A, siRNA, PMP22, C3 mice model, Schwann cells

Proteotoxicity induced integrated stress response in CHCHD10-linked adult-onset neuronopathy

Poster No:
O 507

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Introduction:
CHCHD10 is a mitochondrial protein of unknown exact function, linked to proteotoxicity and several neurodegenerative diseases such as ALS. We previously identified a dominant CHCHD10 variant p.G66V in several families of our cohort of patients having a clinical diagnosis of sensorimotor axonal neuropathy. The entity caused by this CHCHD10 founder mutation, which has a strikingly high prevalence in Finland, is now assigned as spinal muscular atrophy Jokela type (SMAJ).

Methods:
Here, we present our attempts to understand the molecular mechanisms of CHCHD10 p.G66V using various new disease models. We have studied patient serum samples and skin fibroblasts, as well as motor neurons differentiated from patient-specific and genome-edited induced pluripotent stem cells (iPSC), and a novel knock-in mouse model.

Results:
Our results show that the CHCHD10 p.G66V mutant aggregates in fibroblasts and activates the integrated stress response (ISR), leading to metabolic rewiring of the cells. Also the knock-in mice at the age of 12 months present with signs of aggregated CHCHD10 and a mild induction of ISR in skeletal muscle but their motor performance is not affected. Nevertheless, we did not detect induction of ISR in mutant iPSC-derived motor neurons, and our profiling of patients' serum samples indicated that the ISR-linked cytokines FGF21 or GDF15 were not elevated. These findings suggest a cell type specific program in which mutant CHCHD10 leads to proteotoxic responses. Importantly, our knock-in mice do not show a cardiac phenotype in contrast to ALS-CHCHD10 mice, which enables more detailed studies of their neuromuscular function at older ages.

Conclusions:
In conclusion, CHCHD10 p.G66V variant causes a mitochondrial proteotoxicity phenotype, which leads to stress responses variably depending on cell type, and can cause motor-predominant axonal neuropathy with sensory involvement.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: axonal neuropathy, CHCHD10, Mitochondrial integrated stress response, iPSC, Proteotoxicity

Development of CRISPR/Cas9 in vivo therapeutic gene editing for Charcot-Marie-Tooth 1A (CMT1A)

Poster No:
O 508

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Introduction:
Charcot-Marie-Tooth 1A (CMT1A) is the most common inherited neuropathy without a known therapy caused by a 1.4 Mb duplication on human chromosome 17, which includes PMP22 gene. Overexpressed PMP22 is thought to cause demyelination and subsequently axonal degeneration in the peripheral nervous system (PNS). We developed TGT-001, an adeno-associated virus (AAV)-based genome-editing therapeutic candidate encoding Cas9 driven by a novel compact Schwann cell specific promoter and guide RNA (gRNA) to edit TATA-box of Schwann cell-specific P1 promoter of PMP22 to restore normal PMP22 expression.

Methods:
We performed in vivo efficacy assessment of TGT-001 in three different PMP22 overexpressing transgenic models of CMT1A (C22 mice, C3 mice and CMT1A rats) after the onset of disease, using two different routes of administration (intravenous and intrathecal). Furthermore, biodistribution and gene editing efficiency were measured in non-human primates (NHP). Moreover, we utilized Schwann cells differentiated from CMT1A patient derived iPSCs (CMT1A-iPSC-Sch) to assess downregulation of PMP22 level by TGT-001 and its specificity.

Results:
In vivo delivery of TGT-001 in all three animal models of CMT1A demonstrated improvements in neuropathy-related phenotypes including electrophysiological recordings and myelination along with productive gene editing at the TATA-box of P1 promoter of PMP22 and downregulation of PMP22 gene expression level. Therapeutic efficacy throughout all three animal models were greater in intravenous compared to intrathecal injection. NHP delivery of TGT-001 also demonstrated distribution of TGT-001 and productive gene editing in the PNS. In vitro experiments in CMT1A-iPSC-Sch showed downregulation of PMP22 level by TGT-001 and showed no concerning off-target gene editing.

Conclusions:
These results support further development of TGT-001 for CMT1A and additional CRISPR-based therapeutics for other inherited neuropathies.

References:
Yes

References 1:
Lee et al., 2000, Nucleic Acids Research, Volume 48, Issue 1, 10 January 2020, Pages 130–140

References 2:

References 3:

References 4:

Grant Support: This research was supported by Korea Drug Development Fund funded by Ministry of Science and ICT, Ministry of Trade, Industry, and Energy, and Ministry of Health and Welfare (HN22C0431, Republic of Korea)

Keywords: Charcot-Marie-Tooth, Gene therapy, Genetic engineering, CRISPR/Cas9, Translational research

Validating MRI Biomarkers For Clinical Trials In CMT1A Using Automated Segmentation

Poster No:
O 509

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Introduction:
Using our Neuromuscular MRI protocol, we previously demonstrated that lower limb muscle MRI fat fraction is sensitive to detect disease progression in Charcot-Marie-Tooth disease 1A (CMT1A) patients. For approval by regulatory authorities, it will need to be validated against other biomarkers and clinical outcome measures. We aimed to determine whether changes in lower limb muscle fat fraction correlate with CMT examination scores (CMTES) and plasma neurofilament (NfL) and to assess the responsiveness of fat fraction MRI with automated segmentation over 12 months.

Methods:
We recruited 20 patients with CMT1A and 6 controls (further controls recruited as part of a larger MRI study in CMT). Lower limb muscle MRI, CMTES and plasma NfL were acquired at baseline and 12 months. The 3-point-Dixon fat/water separation technique was used to determine thigh and calf muscle fat fraction at a single slice using regions of interest with Musclesense, a trained artificial neural network for lower limb segmentation.

Results:
20 CMT1A patients had baseline lower limb MRI, CMTES and NfL levels. Baseline mean calf fat fraction was increased in CMT1A patients versus controls (22.07±26.51% vs 1.79±0.67%, p 0.003). This increased significantly over 12 months versus controls (1.15±1.77% vs 0.07±0.19%, paired p 0.02). No significant change in CMTES or NfL levels occurred. Standardised response mean (SRM) was 0.65 overall and 1.63 in subgroup whose baseline fat fraction was 10-70%. There was a significant correlation with mean calf fat fraction change and CMTES (r 0.54, p 0.03), which was not detected with NfL.

Conclusions:
Using automated segmentation, we have demonstrated that calf fat fraction remains a responsive biomarker, is superior to clinical outcome measures like CMTES and blood biomarkers like NfL and demonstrates validity by correlation with clinical measures. This study provides further evidence for using lower limb MRI as a biomarker in clinical trials with CMT patients.

References:
No

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References 2:

References 3:

References 4:

Grant Support: The ACT-CMT group acknowledges funding from NIH grant (U01 NS109403). Funding is acknowledged from the National Institute for Health Research University College London Hospitals Biomedical Research Centre (BRC) and British Medical Association (BMA) Vera D

Keywords: CMT, Fat fraction, Biomarker, Outcome measure

Structural context of Charcot-Marie-Tooth disease mutations and homomeric interactions of the Ig domain of MPZ(P0)

Poster No:
O 510

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Introduction:
Different MPZ mutations causing demyelinating or axonal CMT reflect different molecular disease pathways. The extracellular Immunoglobulin-like domain (IgMPZ) of Myelin Protein Zero (MPZ) adheres apposing membranes of the myelin sheath. How IgMPZ forms oligomeric assemblies has been extrapolated from a protein crystal without data confirming how IgMPZ actually oligomerizes in solution, whether homomeric assembly mediates adhesion and myelin biogenesis, or whether loss of oligomerization results in disease. Indeed, mutations throughout the IgMPZ domain give rise to different forms of CMT likely through different disease mechanisms.

Methods:
We used SAXS and NMR to analyze the homomeric association of wildtype IgMPZ. We also spatially mapped patient mutations onto the IgMPZ structure to discern if CMT phenotypes cluster to subregions or surface patches.

Results:
We confirmed that IgMPZ forms cis-tetramers linked via a 'dimer' interface. However, only the tetramer surface predicted by crystal structure data could be disrupted; The dimer interface remains unknown. Spatial mapping uncovered three classes of patient mutations: 1) axonal late-onset disease phenotypes (CMT2) map to the proximal surface residues of IgMPZ near the glycosylation site implying they may be involved in positioning the IgMPZ domain from the membrane; 2) a subgroup CMT1-causing mutations mapped to the IgMPZ interior core, were computationally predicted to de-stabilize the IgMPZ domain structure, and have been found previously to evoke the ER unfolded protein response; 3) other CMT1-causing mutations that map to the distal surface of tetrameric IgMPZ, were not predicted to destabilize the IgMPZ structure, and minimally evoke UPR.

Conclusions:
The correlation of different IgMPZ surfaces mapping to axonal CMT2 or demyelinating CMT1 suggests the dysfunction of distinct protein interaction interfaces as a possible disease mechanism. How these surface mutations might affect oligomerization of MPZ and its adhesion function are unclear since current models for how IgMPZ associates with itself are incomplete.

References:
No

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References 2:

References 3:

References 4:

Grant Support:

Keywords: myelin, MPZ, CMT, phenotype-structure

SORD deficient rats develop a motor-dominant peripheral neuropathy providing novel pathophysiological insights

Poster No:
O 511

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Introduction:
SORD neuropathy is one of the most frequent forms of recessive hereditary neuropathy, affecting approximately 10,000 patients in North America and Europe alone. SORD mutations cause loss-of-function of the enzyme sorbitol dehydrogenase resulting in abnormally high sorbitol. How sorbitol accumulation leads to neuropathy remains to be elucidated. A faithful animal model for SORD neuropathy is essential to study the mechanisms underlying the pathological abnormalities and to develop preclinical studies for potential drugs and gene therapy. Therefore, we have generated a SORD knockout (KO) Sprague Dawley rat to model the human disease and to investigate the pathophysiology underlying SORD deficiency.

Methods:
SORD KO rats were subjected to a battery of behavioral tests to measure motor coordination and strength including rotarod, narrow bean test, grip strength and gait analysis. The neuropathy phenotype was further evaluated by nerve conduction studies (NCS) and comprehensive histology of nerve and other tissues. Biochemical studies were performed to measure sorbitol and neurofilament light chain (NFL) in rat specimens.

Results:
SORD KO rats had remarkably increased levels of sorbitol in serum, cerebral spinal fluid, and peripheral nerve tissue. Moreover, increased levels of NFL, an established biomarker for neurodegeneration, was observed in serum from animals. Motor function impairment in rats was demonstrated by decreased performance with aging in the rotarod and narrow bean tests. Motor nerve conduction velocities of the sciatic and tibial nerve were slowed. Accordingly, histology of the peripheral nerve revealed prominent degeneration of myelinated axons, thin myelin sheaths, and likely pathognomonic, abnormal ballooning split fibers.

Conclusions:
We present the first SORD knockout rodent model developing a motor-dominant peripheral neuropathy that resembles the human phenotype. This model will lead to improved understanding of SORD neuropathy pathophysiology and therapeutic options.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: CMT, rat model, SORD, sorbitol , demyelination

GJB1 Variant Classification

Poster No:
O 512

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Introduction:
Patients with CMTX1, due to variants in gap junction protein beta-1 (GJB1), exhibit a characteristic neuropathy phenotype. However, even when the clinical diagnosis seems certain, many variants are still classified as of 'uncertain significance' (VUS). This could be problematic for trial eligibility or eligibility for preimplantation genetic testing.

Methods:
We analysed in depth, using a modified American College of Medical Genetics (ACMG)/ Association for Clinical Genomic Science (ACGS) criteria, the GJB1 variants carried by patients recruited from 21 international sites from 2009 to 2021.

Results:
421 patients from 324 families were identified as having a variant in GJB1 and/or having CMTX1. Complete variant information was available for 388 patients from 296 families. 157 different variants were identified; this included one male aged 15 years with no neuropathy presenting with a CNS episode (excluded), and two families each carrying two GJB1 variants which were treated as 'combined variants', leaving 154 variants for analysis. We defined 109 (70.8%) variants as pathogenic/likely pathogenic (P/LP) from 244 (82.7%) families, 41 (26.6%) VUS from 47 (15.9%) families and 4 (2.6%) benign variants from 4 (1.4%) families in our cohort. ClinVar classified the same variants as 58.1% P/LP, 41.9% VUS and none as benign.

Conclusions:
We demonstrate that a modified approach to variant classification greatly increases the yield of pathogenic variants with a corresponding reduction in the number of VUS. Two major factors responsible are the inclusion of clinical phenotype and variant segregation data into individual variant classification, confirming that clinical assessment of families is critical to variant interpretation. This will be important when selecting patients for clinical trials.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Charcot-Marie-Tooth, GJB1, CMTX1, genetics, ACMG

Lipid Membrane and Trafficking Dysregulation Contribute to the Pathogenesis of CMT1A

Poster No:
O 513

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Introduction:
Charcot-Marie-Tooth disease (CMT) is the most common inherited neurological disorder of the peripheral nervous system and it's caused by the duplication of the PMP22 gene, which leads to the overproduction of the peripheral myelin protein 22. In this study, we used lipidomics and bulk RNA-sequencing to examine the molecular mechanisms that lead to membrane lipid dysregulation and trafficking alterations in patient-derived induced pluripotent stem cell-derived Schwann cell precursors (iPSC-SCPs) and CMT1A mice

Methods:
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Results:
Bulk RNA-sequencing of sciatic nerves of C3 and C22 CMT1A mice revealed that cholesterol is the most dysregulated pathway throughout their development and that PMP22 overexpression has a dose-dependent suppression on cholesterol metabolism. Similar alterations in lipid metabolism and autophagy were detected in iPSC-SCPs. The lipidomic analysis revealed significant alterations in sphingolipids and specifically a downregulation in sphingomyelins and ceramides in the CMT1A iPSC-SCP compared to their isogenic controls. Interestingly, we also detected an increased membrane disorder in the CMT1A iPSC-SCPs with di-4-ANEPPDHQ flow cytometry analysis. This data indicates possible impaired lipid raft-mediated signaling and lipid transport alterations. Moreover, we detected and enrichment in lipids containing polyunsaturated fatty acids and fatty acids with a long acyl chain. A perfectly balanced ratio between the relative abundance of phosphatidylcholine (PC) and phosphatidylethanolamine (PE) are critical parameters of cellular health. From the lipidomics analysis we observed and altered PC/PE ratio in the CMT1A iPSC-SCPs, thus increasing the evidences of myelin dysfunctions in the disease

Conclusions:

As the lipid composition varies drastically during postnatal development, these results indicate that the overexpression of PMP22 impacts specific lipid classes, mostly sphingolipids, leading to membrane and storage lipid dysregulation. These changes may contribute to the pathogenesis of CMT1A by disrupting the initiation of myelination or its structural integrity

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: CMT1A, Lipidomics, Schwann cell, Lipid metabolism

Blood-neural barrier impairments drive TRPV4-mediated neurodegenerative disease

Poster No:
O 514

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Introduction:
Missense mutations of the polymodal, calcium-permeable cation channel TRPV4 cause forms of distal spinal muscular atrophy and Charcot-Marie-Tooth disease. While disease-causing mutations in TRPV4 increase channel activity *in vitro*, little is known about how expression of mutant TRPV4 channels *in vivo* precipitates neurodegeneration.

Methods:
To gain insights into the cellular basis of TRPV4-mediated neuromuscular disease, here we generated and characterized two knock-in mouse lines in which different disease-causing mutations (R269C, R232C) were introduced into the endogenous mouse *Trpv4* gene.

Results:
TRPV4 mutant mice exhibited marked motor behavioral impairments, motor neuron loss at select cervical spinal cord levels, and lethality by weaning age. Strikingly, selective genetic deletion of mutant TRPV4 from endothelial cells (but not neurons, muscle, or glia) abrogated each of these phenotypes. Assessments of blood-neural barrier (BNB) integrity in symptomatic mutant mice revealed focal BNB disruptions in the cervical spinal cord ventral horn and brainstem. Coincident with BNB breech, deficits in cervical spinal cord neurotransmission were observed, including diminished monosynaptic reflexes. Analysis of *Trpv4* reporter mice demonstrated that TRPV4 expression within the nervous system occurs primarily in endothelial cells. Furthermore, neural endothelial cells isolated from mutant mice exhibited elevated TRPV4 channel activity. Given these findings, we investigated the capacity of TRPV4-specific antagonists to ameliorate phenotypes in mutant mice. Systemic administration of the TRPV4 antagonist GSK2193874 abrogated the BNB impairments of symptomatic mutant mice and, importantly, provided a pronounced rescue of the motor behavioral and lethality phenotypes.

Conclusions:
Here, we identify focal impairments of endothelial cell function and BNB integrity as key drivers of TRPV4-mediated neuropathology *in vivo*. Together, these findings reveal a novel pathogenic role of TRPV4 in neural endothelial cells, highlight the reversibility of phenotypes in mutant TRPV4 mice, and provide evidence that small molecule antagonism may represent a potential disease-modifying therapeutic strategy for patients with TRPV4 mutations.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Charcot-Marie-Tooth disease, TRPV4, blood-neural barriers, motor neurons, endothelial cells

Preclinical Studies of Pharmacological and Gene Therapy Treatments in Mouse Models of CMT2D

Poster No:
O 515

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Institutions:
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Introduction:
CMT-associated dominant mutations in tRNA synthetase genes activate the integrated stress response (ISR) through the sensor kinase GCN2. Inhibiting GCN2 at or before disease-onset prevents ISR activation and mitigates neuropathy. We provide additional preclinical data on GCN2 inhibition and demonstrate efficacy of a novel gene therapy in mouse models of Gars/CMT2D.

Methods:
We performed two studies using an experimental GCN2 inhibitor (GCN2iB) in Gars-ΔETAQ mice modeling CMT2D: 1) mice were treated post-onset; 2) mice were treated at disease-onset, but treatment stopped after 4 weeks to test necessity of life-long treatment. A separate cohort was treated neonatally with a novel gene therapy approach

Results:
When treatment with GCN2iB was started post-onset (P35) and continued for 5 weeks, Gars-ΔETAQ mice showed improvement over the course of the study, gaining body weight, improving motor performance and showing better neurophysiological outcomes. The basis for this improvement is under investigation, but the ability of the drug to improve function post-onset is important. In a second cohort, treatment was started at disease onset (P14) and continued for 4 weeks, then stopped and mice followed for an additional 4 weeks. These mice showed an improvement in motor performance during the treatment phase and some neurophysiological benefit persisted even four weeks after treatment ended, but motor performance declined when treatment stopped. Therefore, continued treatment is likely required to maintain benefit. In a separate test of a novel gene therapy, Gars-ΔETAQ mice treated neonatally performed at near-wild-type levels in neurophysiological and motor tests as adults.

Conclusions:
Inhibiting GCN2 is beneficial in mouse models of CMT2D even when treatment is started post-onset, improving the potential relevance of this approach for patients. However, maintaining benefit requires continued treatment. When given neonatally, our novel gene therapy substantially mitigated neuropathy, thus providing a second candidate therapeutic strategy for tRNA-synthetase-induced CMT.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: NINDS R37NS054154

Keywords: CMT, Gars, tRNA synthetase, GCN2, gene therapy

Modelling human neuromuscular junctions in axonal Charcot-Marie-Tooth disease using co-cultures and neuromuscular assembloids

Poster No:
O 516

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Introduction:
In the past decade, a number of in vitro human cellular models have been used to study and characterize Charcot-Marie-Tooth (CMT) neuropathy. However, most cell models consisted of traditional two-dimensional monoculture induced pluripotent stem cell (IPSC)-derivatives. Although useful, an important and poorly investigated hallmark are deficits at the neuromuscular junctions (NMJs), bridging the peripheral nerve and muscle. We aimed to develop a human neuromuscular model to characterize the role of NMJs in axonal CMT.

Methods:
We differentiated motor neuron spheres from human iPSCs from the most common axonal subtype of CMT disease, CMT2A, along with an isogenic control. In addition, we differentiated primary human muscle cells to generate co-cultures and 3D neuromuscular assembloids.

Results:
We developed a motor neuron sphere-muscle co-culture as well as a 3D neuromuscular assembloid model, the latter by fusing the motor neuron sphere with a differentiated human muscle sphere. These models contained NMJs, confirmed by the presence of α-Bungarotoxin (αBTX) and bassoon (presynaptic multi-domain protein) as active-zone marker using immunocytochemistry. These models are currently being used to study NMJs in axonal CMT.

Conclusions:
The generation of a human neuromuscular model could provide novel insights into the disease mechanisms and could be of great interest not only for CMT therapy development, but could also be relevant for other neuromuscular diseases.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Charcot-Marie-Tooth neuropathy , iPSCs, Neuromuscular junctions, Co-cultures , Neuromuscular assembloids

Myelin Maturation In Rat Sciatic Nerve: A Lesson From A CMT1A Model

Poster No:
O 517

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Introduction:
Myelin membrane has been traditionally considered a stable insulating sheath around the axon fundamental to optimize conduction of action potentials over long distances. Indeed, it has been recently shown that myelin performs upper roles in the nervous system displaying remarkable plasticity. Mainly proved in the CNS, myelin plasticity is referred as the subtle and specific changes in myelin quantity, structure and chemical composition that occur in time, diseases or after a stimulus.

Methods:
Here, we monitored myelin changes regarding structure and chemical composition in rat sciatic nerves during normal development and in a model of inherited dysmyelinating neuropathy, the CMT1A rat. Using an up-to-date omics approach, we analysed lipid composition of myelin fraction purified by sciatic nerves between 5 and 365 days after birth. We also performed, at the same time points, an advanced morphometric analysis on more than 100.000 myelinated nerve fibres, each assessed for 14 different variables. Data from composition and structure of normal and pathological myelin overtime were matched and analysed by integrative statistics.

Results:
We found that during normal development myelin undergoes a continuous maturation both in lipid composition and physical structure. Of note, CMT1A adult myelin was unable to properly carry out the maturation process, displaying an arrest between 10 and 20 days after birth. These data were also confirmed by the trend of small hyper-myelinated fibres, one of the CMT1A hallmarks, that we found to be present in immature normal nerves.

Conclusions:
In conclusion, our results imply myelin plasticity also in the PNS both in healthy and pathological condition; moreover, we demonstrated that the dysmyelinating CMT1A phenotype is due to an arrest of the CMT1A myelin maturation. Overall, this study suggests novel perspectives underlying the myelinopathy in CMT1A and the way to effectively address this issue.

References:
Yes

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Visigalli D, Capodivento G, Basit A, Fernández R, Hamid Z, Pencová B, Gemelli C, Marubbi D, Pastorino C, Luoma AM, Riekel C, Kirschner DA, Schenone A, Fernández JA, Armirotti A, Nobbio L. Exploiting Sphingo- and Glycerophospholipid Impairment to Select Ef

References 2:

References 3:

References 4:

Grant Support:

Keywords: Myelin, CMT1A, Myelin Plasticity, Lipidomics analysis, Morphometric analysis

Development of Guidelines on Defining and Monitoring Progression of ATTRv Amyloidosis Using the Delphi Technique

Poster No:
O 518

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Institutions:
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Introduction:
Hereditary transthyretin amyloidosis (ATTRv) is an inherited, progressively debilitating, and life-threatening disease with multisystem involvement, resulting in a mixed phenotype presentation of polyneuropathy and cardiomyopathy. There is currently no cure, but treatment can delay progression. Guidelines for monitoring disease progression are limited and globally applicable guidelines are needed. This study aimed to establish best practice guidelines for defining and monitoring disease progression of ATTRv amyloidosis.

Methods:
A literature review aided development of an interview guide through identification of key topics in defining and monitoring disease progression of ATTRv amyloidosis. Qualitative interviews were conducted with five expert clinicians involved in the care of patients with ATTRv amyloidosis to develop draft guidelines. Eight expert clinicians (five neurologists, three cardiologists) participated in the Delphi panel and reviewed the guidelines via an online survey across three rounds, with a post round-three review of one statement to ensure sufficient consensus. Five patient advocates were recruited to review the draft and final guidelines to incorporate the patient perspective.

Results:
The interviews identified 82 signs/symptoms, 85 assessments/tools to monitor ATTRv amyloidosis, and 19 thresholds indicating progression which informed the initial guidelines reviewed by patient advocates and subsequently presented in the Delphi panel. Across three rounds, consensus improved and fewer modifications were made. Following the final round, consensus was achieved for 24/26 statements/tables included within the guidelines with consensus likely not being met for two statements due to the expert clinicians having different specialties resulting in them responding neutrally to the inclusion of the statements. Minor adjustments were made following the final clinician review and patient advocate feedback.

Conclusions:
This study generated consensus on defining and monitoring disease progression of ATTRv amyloidosis resulting in clinician- and patient advocate-approved guidelines. The final guidelines are intended for use

in clinical practice worldwide to direct decision-making in clinical management of patients with ATTRv amyloidosis.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: ATTRv amyloidosis, disease progression, monitoring, Delphi consensus

Tyrosyl-tRNA Synthetase Has a Non-canonical Function in Actin Bundling

Poster No:
O 519

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Introduction:
Dominant mutations in tyrosyl-tRNA synthetase (YARS1) and six other tRNA-ligases cause Charcot-Marie-Tooth peripheral neuropathy (CMT). Loss of aminoacylation is not required for their pathogenicity, suggesting a gain-of-function disease mechanism.

Methods:
Genetic, behavioral, immunohistochemical, electrophisiological and morphological studies were performed in Drosophila. Biochemical studies were done using recombinant YARS1, GARS1, HARS1, DARS1 and Plastin-3 proteins. Immunohistochemistry and actin remodeling experiments were designed in human SH-SY5Y neuroblastoma cells and patient-derived fibroblasts.

Results:
By an unbiased genetic screen in Drosophila, we link YARS1 dysfunction to actin cytoskeleton organization. Biochemical studies uncover yet unknown actin-bundling property of YARS1 to be enhanced by a CMT mutation, leading to actin disorganization in the Drosophila nervous system, human SH-SY5Y neuroblastoma cells, and patient-derived fibroblasts. Genetic modulation of F-actin organization by another actin-bundling protein (Fimbrin) improves hallmark electrophysiological and morphological features in neurons of flies expressing CMT-causing YARS1 mutations. Similar beneficial effects are observed in flies expressing a neuropathy-causing glycyl-tRNA synthetase.

Conclusions:
Im this stidy, we show that YARS1 is an evolutionary-conserved F-actin organizer which links the actin cytoskeleton to tRNA-synthetase-induced neurodegeneration.

References:

Yes

References 1:
Ermanoska et al., Nature Communications 2023, in press

References 2:

References 3:

References 4:

Grant Support: This work was supported by funding from the University of Antwerp to AJ and VT. The Fund for Scientific Research-Flanders: G048220N and G0A2122N to AJ, G041416N to VT. The Belgian Association Against Neuromuscular Diseases grants to AJ, MLPE, VT. The Amer

Keywords: CMT, Drosophila, aminoacyl-tRNA synthetases, actin demodeling, disease mechanism

International Diabetes Neuropathy Consortium

International Diabetes Neuropathy Consortium (IDNC) Abstracts

O 520 - 531

Identification of Clinical and Genetic Mortality Risk Factors in Patients with Diabetic Autonomic Neuropathy

Poster No:
O 520

Authors:
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Institutions:
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Introduction:
Patients with diabetic autonomic neuropathy (DAN) are at higher risk for silent myocardial ischemia and sudden cardiac death. We sought to identify mortality risk factors in DAN patients.

Methods:
124 patients were followed for up to 345 weeks after a diagnosis of symptomatic DAN based on clinical evaluation and autonomic testing. Autonomic testing results, clinical data obtained near autonomic testing, and genotypes (N=68) at rs7294345 and rs147738081, previously associated with idiopathic polyneuropathy, were analyzed retrospectively to identify characteristics differing between surviving (N=99) and non-surviving (N=25) patients. Kaplan-Meier and Cox proportional hazards analyses identified mortality risk factors.

Results:
The time from autonomic testing to death in non-survivors was shorter than the time to the last follow-up in survivors (110.6 69.4 versus 160.6 88.5 weeks, p=0.002). Non-survivors were older (72.7 12.8 versus 64.5 13.2 yr, p=0.003), had lower body mass index (BMI, 26.5 5.3 versus 20.65 6.7, p=0.001), longer diabetes duration (25.0 15.7 versus 19.3 12.1 yr, p=0.049), more cardiac disease (84% vs 70%, p=0.001), specifically cardiac arterial disease (60% vs 33%, p=0.014), head-up tilt test abnormalities (96% vs 76%, p=0.030), neurogenic orthostatic hypotension (84% vs 27%, p<0.0001) and abnormal QSART (72% vs 48%, p=0.039). Clinically, survivors and non-survivors often were similarly affected, having <5th percentile scores on autonomic tests, somatic diabetic neuropathy, abnormal glycosylated hemoglobin (HbA1c) and creatinine levels. In unadjusted analyses, DAN diagnosis age (HR[95% CI]: 1.05[1.02–1.10], p=0.003], diabetes duration (1.03[1.004–1.06], p=0.024), BMI (0.88[0.82–0.95], p=0.001), history of stroke (2.79[1.19–6.54]), p=0.019), cardiac disease (3.98[1.36–11.60], p=0.011), neurogenic orthostatic hypotension (6.98[2.39–20.35], p<0.0001), abnormal QSART (2.582[1.08–6.19], p=0.034) and rs41526435 TC (proxy for rs147738081 CT, 5.72[1.62-20.19]. p=0.007) significantly increased mortality risk. In adjusted analyses, BMI [0.88[0.81–0.96), p=0.004] and neurogenic orthostatic hypotension (6.01[1.86–19.45], p=0.003) remained significant.

Conclusions:
These findings can inform guidelines for multifactorial risk control to reduce mortality in DAN patients.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: This work was supported by the Agency for Healthcare Research and Quality (R01HS024057) awarded to Demetrius Maraganore and the generous funding support of the Auxiliary of NorthShore University HealthSystem.

Keywords: Diabetic autonomic neuropathy, Increased mortality, Genetic marker, Autonomic testing, Neurogenic orthostatic hypotension

Evaluation of Nicotinamide Riboside in Prevention of Small Fiber Axon Degeneration and Promotion of Nerve Regeneration

Poster No:
O 521

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Introduction:
Recent advances in understanding what mediates Wallerian degeneration showed that several genes (e.g. NMNAT2, Sarm1) and NAD+ metabolites play a key role in degeneration of axons in a distal-to-proximal manner seen in many peripheral neuropathies. Pre-clinical studies have shown that rapid depletion of NAD+ initiates a cascade of molecular events that lead to axon degeneration and that supplementation of a NAD precursor, nicotinamide riboside (NR), can prevent this degeneration.

Methods:
In this Phase 2 placebo-controlled study (Clinicaltrials.gov, NCT03912220) we aimed to evaluate the ability of NR to prevent degeneration of small somatic sensory axons innervating the epidermis, as well as its ability to promote regeneration of these same fibers. We applied 0.1% capsaicin cream for 48 hours to a small area on the outer thigh of fifty healthy volunteers. Intraepidermal Nerve Fiber Density (IENFD) was determined by collecting skin biopsies before and at three different times (2, 60 and 90 days) after capsaicin was applied. Two additional skin biopsy samples were collected, one before the participants started taking study drug and the second one after they were taking study drug for about a week to evaluate if the intake of NR has any effects on gene expression. In addition, blood samples were collected to measure plasma NAD+ levels.

Results:
All the participants have been enrolled and last study participants are scheduled to complete the study during the first quarter 2023. Results will be available for the PNS meeting in June 2023.

Conclusions:
Conclusions will be available for the PNS meeting in June 2023.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: Funding provided by Adelson Foundation

Keywords: small nerve fibers, treatment, nicotinamide riboside , clinical trial, nicotinamide adenine dinucleotide

Muscarinic Receptor Antagonism Activates TRPM3 to Augment Mitochondrial Function and Neurite Outgrowth in Sensory Neurons

Poster No:
O 522

Authors:
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Introduction:
Diabetic peripheral neuropathy (DPN) comprises a dying-back axonal degeneration leading to sensory loss and neuropathic pain. We are developing strategies to drive regeneration of sensory neurons by blocking the muscarinic acetylcholine type 1 receptor (M1R). M1R antagonism induces a slow increase of intracellular Ca2+ that activates AMP-activated protein kinase (AMPK) and stimulates mitochondrial function and neurite outgrowth. A potential source of Ca2+ is the transient receptor potential channel 3 (TRPM3) that is closed under low phosphatidylinositol biphosphate (PIP2) levels. We hypothesized that M1R antagonism-induced blockade of G protein signaling leads to PIP2 levels rising and triggering activation of TRPM3.

Methods:
Adult dorsal root ganglion (DRG) sensory neurons derived from age-matched or type 1 streptozotocin (STZ)-induced diabetic rats were cultured and treated with TRPM3 agonists, CIM0216 and pregnenolone sulphate (PS). Ca2+ homeostasis, mitochondrial function and neurite outgrowth were analyzed using microscopy, Western blot and Seahorse XF24. The metabolomic profile was evaluated to assess cellular metabolism. Adeno-associated virus (AAV) delivered shRNA to specifically down-regulate TRPM3 expression.

Results:
TRPM3 inhibitors - primidone or isosakuranetin – blocked Ca2+ influx induced by TRPM3 agonists. In cultures derived from M1R knockout mice the effect of TRPM3 agonism was suppressed. TRPM3 agonists activated AMPK, elevated mitochondrial function and augmented neurite outgrowth. AAV delivery of shRNA to TRPM3 blocked the stimulatory effect of CIM0216 or PS on AMPK phosphorylation. Selective M1R antagonism by pirenzepine elevated neurite outgrowth and this process was suppressed by TRPM3 knockdown. Untargeted metabolomics analysis exhibited enrichment in galactose and pyruvate metabolism induced by TRPM3 agonists and supported the stimulation of neuronal bioenergetics.

Conclusions:
These novel results reveal that TRPM3 channels mediate the effect of M1R antagonism on mitochondrial function and neurite growth. These findings support ongoing clinical trials with M1R antagonists in persons with peripheral neuropathies and DPN. Funded by CIHR grant # PJT-162172.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: Funded by CIHR grant # PJT-162172

Keywords: Neuronal Regeneration, Diabetic peripheral neuropathy, Mitochondrial function, Metabolomics, Calcium imaging

Schwann Cell-Derived Extracellular Vesicles Drive Nerve Insulin Resistance in Peripheral Neuropathy

Poster No:
O 523

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Introduction:
The prevalence of prediabetes and type 2 diabetes is increasing worldwide due in part to the overconsumption of energy-dense foods and a sedentary lifestyle. Peripheral neuropathy (PN) is a common complication of both disorders and can lead to pain, amputations, and a reduced quality of life. Schwann cells (SCs) maintain axonal health under homeostatic conditions through the transfer of extracellular vesicles (EVs), and contribute to damage in PN, via mechanisms that remain undefined. Here, we aimed to investigate the role of SCs and SC-derived EVs in in vivo and in vitro models of prediabetes, type 2 diabetes, and PN.

Methods:
We first used single-cell RNA sequencing to interrogate the contribution of SC subsets and their transcriptomic signatures to PN in the high-fat diet fed mouse, which mimics human PN. Then, using in vitro PN models, we examined the effects of EVs isolated from palmitate-treated SCs on neuronal insulin signaling and resistance.

Results:
Single-cell RNA-sequencing identified four major SC clusters, myelinating, non-myelinating, precursor, and repair, in healthy and neuropathic nerves, in addition to a distinct cluster of nerve macrophages. Particularly, we found that myelinating SCs become insulin resistant in response to prediabetes. Additional validation analyses revealed that damaged SCs release pathologic EVs, carrying miR-15b, a key regulator of lipid metabolism and insulin resistance. When taken up by neuronal cultures, these EVs are sufficient to induce insulin resistance, which may contribute to PN pathogenesis.

Conclusions:
Overall, our research highlights the role of EV-mediated communication as a mechanism by which SCs support axons, beyond myelination. It further suggests that SC dysfunction can disrupt SC-axon communication, ultimately leading to nerve degeneration and PN.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: Funding was provided by the National Institutes of Health (NIH) (R01DK130913, 1R24082841 to J.H. and E.L.F.); Novo Nordisk Foundation (NNF14OC0011633 to E.L.F.), the Nathan and Rose Milstein Research Fund (to S.A.E), Neuronetwork for Emerging Therapies at

Keywords: Schwann cells, extracellular vesicles, insulin resistance, mouse, peripheral neuropathy

Increased Persistent Na^+ Currents In Addition To The Depolarizing Changes Of Myelinated Axons In Type 2 Diabetes Mellitus

Poster No:
O 524

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Institutions:
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Introduction:
Myelinated axon excitability studies in diabetes mellitus revealed small and inconsistent abnormalities with little mechanistic insight other than a slight membrane depolarization. The aim of this study was to investigate the excitability of myelinated axons in a series of patients with type 2 diabetes mellitus under monotherapy with metformin.

Methods:
Investigations were carried out in 14 patients with type 2 diabetes (age 43-78 years) as compared to a group of 42 healthy controls (age 35-75 years). Total Neuropathy Score and Modified Toronto Clinical Neuropathy Score were used to assess the neuropathy severity. Conventional nerve conduction studies were done to exclude carpal tunnel syndrome. Multiple measures of axonal excitability by threshold tracking were carried out by stimulating the median nerve at the wrist. Compound muscle action potentials were recorded from abductor pollicis brevis. Antidromic compound sensory action potentials were recorded from digit II.

Results:
In the patients, the sensory axons showed an increase in the strength-duration time constant (SDTC) from 0.548 ms to 0.646 ms associated with smaller threshold deviations during depolarizing electrotonus, measured by a reduction in TEd(90-100ms) from 49% to 45%. Both abnormalities were consistent with membrane depolarization. Consistently, the motor axons of the patients showed an increased SDTC from 0.435 ms to 0.496 ms. Nevertheless, in the patients, the TEd(90-100ms) was increased from 47% to 50%, and not decreased like in the sensory axons. Mathematical simulations using the Bostock nodal-internodal axon model suggested that this discrepancy could be accounted for by an increase in the persistent Na^+ current, independent of the changes in the membrane potential. The SDTC abnormality increased in patients with poor glycaemic control.

Conclusions:
Our data suggest that in type 2 diabetes mellitus, myelinated axons show an increase in the persistent Na^+ currents beyond the membrane depolarization that could be attributed to the energy insufficiency of the Na^+/K^+ pumps.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Diabetes, Axon excitability, Membrane potential, Sodium channels, Mathematical modeling

Chronic Axonal Polyneuropathy In The General Population: Update From The Rotterdam Study

Poster No:
O 525

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Institutions:
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Introduction:
Chronic axonal polyneuropathy (CAP) is a common disease with a prevalence of 1% to 7% worldwide and 3.3% in the Netherlands. The morbidity is considerable, with strong interference in daily life activities. The aim of this population-based study is to investigate epidemiological factors including new, or potentially modifiable risk factors for CAP.

Methods:
This study is part of the Rotterdam Study, a population-based cohort study running since 1990 that aims to study chronic diseases in the general population aged >40 years old. Participants undergo extensive tests every 3-5 years, and since June 2013 a polyneuropathy screening has been implemented. The screening consists of three components: a symptom questionnaire, neurological examination, and nerve conduction studies of the legs. Based on this information, participants are categorized in consensus-meetings as definite, probable, possible, or no polyneuropathy.

Results:
From June 2013 until January 2020, 4453 participants were screened of whom 271 were excluded due to insufficient data. Of the remaining 4182 participants (54.9% female), 4.3% (N=181) had definite, 5.3% (N=221) probable, 19.1% (N=798) possible, and 71.3% (N=2982) had no polyneuropathy. Participants with definite polyneuropathy were more often male (52.5% vs. 47.5%). On average, participants with polyneuropathy were older than participants with no polyneuropathy (76 years vs. 62 years). The number of participants undergoing re-screening (now 250) is increasing, allowing us to study the incidence and early features related to the development of CAP in the future. Other potentially modifiable risk factors, including obesity and chronic medication use will be investigated.

Conclusions:
CAP is a common disease in the general population. Both cross-sectional and longitudinal studies are needed to identify risk factors and to better understand relevant factors in the etiology of CAP. The search for risk factors for polyneuropathy is important since this potentially enables to modify or even prevent CAP in the future.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Chronic axonal polyneuropathy, Risk factors, Prevalence

Human-derived Co-culture System to Study Factors Affecting the Sensory Axon-Skin Interaction in Diabetic Peripheral Neuropathy

Poster No:
O 526

Authors:
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Institutions:
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Introduction:
One of the salient characteristics of diabetic peripheral neuropathy (DPN) is the dying back of sensory axons from the skin. Additionally, DPN patients have decreased axonal regeneration within skin compared to healthy controls (1-3). It is poorly understood what is responsible for nerve degeneration and impaired axonal plasticity in DPN. Is it the diabetic environment that inhibits axon growth, a reduced axonal capacity, or both? A plausible hypothesis is that the epidermis from people with diabetes acts as an inhospitable environment for axonal sprouting. Alternatively, factors intrinsic to sensory axons of DPN patients might result in diminished growth.

Methods:
To study the sensory axon-skin interaction in vitro, we have established a spatially separated co-culture system of human induced pluripotent stem cell (iPSC)-derived sensory neurons and skin tissue biopsies. Human iPSCs are differentiated into sensory neurons which are cultured in the cell body compartment of microfluidic devices. Their axons extend through microchannels into a separate compartment to isolate the axons away from cell bodies for study. Tissue slices from patient skin biopsies are also cultured within this axonal compartment, which allows us to analyze the distal axon-skin interaction.

Results:
We have matured and cultured iPSC-derived sensory neurons in these devices and have observed long axons extending up to ~3 mm in length. We have determined successful generation of mature sensory neurons by staining for Islet1, BRN3A, NaV1.7, and NaV1.8. Additionally, we have cultured skin tissue sections from skin-punch biopsies within the axonal compartment of these devices, with skin surviving structurally intact.

Conclusions:
We have established a human-derived co-culture system to study the sensory axon-skin interaction in DPN patient vs control cell lines and tissue, giving us a way to better ascertain what factors (diabetic environment within the skin or inherent neuronal trait) lead to the degeneration and diminished regenerative capacity in DPN patients.

References:
Yes

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References 4:

Grant Support: R21NS125783 National Institute of Health (NIH)/NINDS

Keywords: Diabetic Peripheral Neuropathy, Sensory Neurons, iPSCs, Skin, Microfluidics

Longitudinal Changes in Serum Neurofilament Light Chain Levels in Diabetic Polyneuropathy

Poster No:
O 527

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Institutions:
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Introduction:
There is a lack of easily applicable objective tools facilitating detection and follow-up of diabetic polyneuropathy (DPN). We investigated longitudinal serum levels of the axonal biomarker neurofilament light chain (s-NfL) in people with type 2 diabetes (T2D) to clarify the potential of s-NfL as a biomarker for DPN.

Methods:
We performed a nested case-control study of a subgroup of the ADDITION-Denmark cohort of people with screen-detected T2D examined clinically 5 and 10 years after their diabetes diagnosis (N=178). Based on Toronto criteria for clinically confirmed DPN at the 10-year examination, we divided the group into participants with and without DPN. Biobank serum samples from both time points were analysed for s-NfL using single-molecule array (Simoa®).

Results:
Median s-NfL levels increased from the 5- to the 10-year examination both in participants with DPN (11.3 ng/L (IQR 9.54; 15.6 ng/L) to 18.8 ng/L (IQR 14.4; 27.9 ng/L), $p< 0.001$, N=39) and in participants without DPN (10.2 ng/L (IQR 7.49; 13.7 ng/L) to 15.4 ng/L (IQR 11.7; 20.1 ng/L), $p<0.001$, N=139). The increase in s-NfL in participants with DPN was greater than in those without DPN (median Δs-NfL 7.4 ng/L (IQR 3.8; 12.9 ng/L) vs. 4.7 ng/L (IQR 2.8; 8.1 ng/L), $p=0.03$). Participants with DPN had higher s-NfL at both 5 and 10 years (19.5% (95% CI 0.6; 41.9%) and 26.1% (95% CI 6.6; 49.1%) higher s-NfL, respectively). The group difference remained significant through adjustment for age, sex, ADDITION-randomization group, BMI and eGFR at 10 years, but not at 5 years. The risk of DPN increased with higher s-NfL at 5 years (OR 1.18 (95% CI 1.00; 1.38) for a 3 ng/L increase in s-NfL) but did not remain significant after adjustment for covariates.

Conclusions:
The findings suggest that s-NfL may represent a biomarker for DPN and a potential factor in predicting DPN.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: This work was supported by a research grant from the Danish Diabetes Academy, which is funded by the Novo Nordisk Foundation, grant number NNF17SA0031406. Additional support was received by the A.P. Møller Foundation, The Riisfort Foundation and the Depar

Keywords: diabetic polyneuropathy, neurofilament light chain, type 2 diabetes, biomarkers

The association between longitudinal metabolic trajectories and peripheral neuropathy

Poster No:
O 528

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Introduction:
The aim of this study was to determine the association between longitudinal trajectories of metabolic risk factors and peripheral neuropathy in individuals with longstanding diabetes.

Methods:
We performed a longitudinal study following American Indians with type 2 diabetes. From 1988-2013, participants completed approximately annual assessments of metabolic risk factors, including BMI, HbA1c, systolic blood pressure (SBP), triglyceride, and high-density lipoprotein cholesterol (HDL) measurements. From 2013-2019, participants completed annual neuropathy assessments using the Michigan Neuropathy Screening Instrument (MNSI) combined index. For each metabolic risk factor, from 1988-2013 we calculated the: (a) rate of metabolic change; and (b) area under the metabolic trajectory. Mixed effects regression was used to evaluate the associations between these longitudinal metabolic trajectories (i.e., rate of change and area under the trajectory) and peripheral neuropathy.

Results:
We enrolled 89 participants (77.5% female) with type 2 diabetes that were followed for a mean (standard deviation [SD]) of 14.2 (10.2) years between 1988-2019. At the time of the first neuropathy assessment, the mean age was 54.6 (10.1) years and mean diabetes duration was 25.1 (6.4) years. Regression models revealed that a faster rate of BMI increase (between 1988-2013) associated with higher first MNSI index (in 2013) after adjusting for age, sex, diabetes duration, and height (Point Estimate [PE]: 427.6, 95%CI: 91.3,763.8). In contrast, a faster rate of HbA1c increase was associated with a lower MNSI index (PE: -1622, 95%CI: -2413,-830). Neither area under the BMI or HbA1c curves associated with neuropathy. In addition, longitudinal trajectories of SBP, triglyceride, and HDL measurements did not associate with neuropathy.

Conclusions:
We found that increases in BMI are associated with neuropathy progression. This highlights the importance of interventions to prevent worsening of obesity to potentially improve neuropathy outcomes in individuals with longstanding diabetes. The progression of neuropathy with improved glycemic control deserves further study.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: Dr. Reynolds is supported by the NIH NIDDK (K99DK129785). Dr. Nelson is supported by The Intramural Research Program of the National Institute for Diabetes, Digestive and Kidney Disease. Dr. Callaghan is supported by the NIH NIDDK (R01DK115687). Dr. Feldm

Keywords: peripheral neuropathy, longstanding diabetes, metabolic risk factors trajectories, obesity, metabolic syndrome

Noninvasive Visualization of Free Intraepidermal Nerve Endings for Realtime Diagnosis of Small Fiber Neuropathy

Poster No:
O 529

Authors:
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Institutions:
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Introduction:
Skin biopsy was the current gold standard to provide free-intraepidermal-nerve-endings (FINEs) structural information for the differential diagnosis of small fiber neuropathy (SFN). However, its invasive nature was particularly unfavorable for diabetic neuropathy patients with coagulation abnormalities. Here we present a three-dimensional nonlinear optical imaging method, called FINEscope, for noninvasive FINEs imaging, especially designed and applied for the terminal distal extremities. Clinical study results on differential diagnosis of diabetic peripheral neuropathy (DPN) are presented.

Methods:
The label-free and pathological capability of FINEscope was first confirmed by PGP9.5 immunohistochemistry staining and followed by an in vivo longitudinal spared nerve injury model study. Moreover, through proposing a dot-connecting algorithm, we established the protocol to count three-dimensionally the intraepidermal nerve fibers (IENF) and define the quantitative IENF index.

Results:
The proposed FINEscope was shown to be able to delineate the 3D structure of unmyelinated FINEs that are confirmed by PGP 9.5 immunohistochemistry staining from the same tissue section of human skin. With longitudinal tracking in the SNI animal model, the observed nerve-like signals at baseline disappeared completely 48 hours after nerve injury. Moreover, our in vivo clinical trial showed that the label-free IENF index can differentially identify SFN (P-value=0.0102) and was well correlated with IENF density of skin biopsy (Pearson's correlation, R-value= 0.98) in the DPN group.

Conclusions:
Our study confirm that the unstained FINEscope imaging can noninvasively provide FINEs structure information assisting diagnosing small fiber neuropathy. This non-invasive imaging system would meet the clinical need for a free nerve endings imaging tool not only to assist the screening and differential diagnosis of DPN but also for surgical evaluation and efficacy assessment of radiculopathy treatment and therapy in the future.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: This work was sponsored by National Science and Technology Council under MOST 107-2321-B-002-006, MOST 110-2221-E-002-048-MY3, and Ministry of Economic Affairs under 111-EC-17-A-19-S6-009.

Keywords: Free Nerve Endings, Small Fiber Neuropathy, diabetic peripheral neuropathy, label-free imaging, optical biopsy

Useful And Cost-effective Workup In Chronic Polyneuropathy (The EXPRESS Study)

Poster No:
O 530

Authors:
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Introduction:
Polyneuropathy is a common disease that has many causes and risk factors. The evidence-based Dutch guideline Polyneuropathy recommends to conduct a complete workup, despite knowledge gaps regarding the usefulness and extent of blood tests and nerve conduction studies (NCS). Our hypothesis is that in many patients with a clinical diagnosis of chronic polyneuropathy, a limited or no further workup improves cost-effectiveness without loss of diagnostic reliability.

Methods:
The EXPRESS study is a prospective observational multi-center study carried out in five large general hospitals and three neuromuscular expertise centers. Adult patients with symptoms suspect for polyneuropathy, who are referred to a neurologists for an outpatient workup are eligible. Patients' electronic medical records (EMR) are used to gather all relevant data. Direct medical costs and other health care costs are determined from these data and questionnaires. The total sample size will be 1200 patients. Real-time workup by patients' neurologists will be compared to a hypothetical limited or no further workup by a panel of neurologists with experience in neuromuscular diseases. To assess generalizability of the findings, general neurologists in the participating hospitals also performed a hypothetical workup in a random subset of 300 cases and these results will be compared with the evaluation of the panel using inter-rater kappa analysis. Each patient is his own control and follow-up time is 6 months.

Results:
Primary outcome is effectiveness of a limited or no further workup expressed as concordance between panel diagnosis and patients' neurologists diagnosis (i.e. percentage overlooked diagnoses). We will report patient demographics and concordance in diagnosis established through real-time workup by patients neurologists and diagnosis by hypothetical limited or no workup.

Conclusions:
This study will provide clarity about cost-effective workup to establish the diagnosis and etiology in patients with chronic polyneuropathy.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: ZonMW ZE&GG grant

Keywords: Polyneuropathy, Cost-effective workup, Limited workup

Local Retinoblastoma1 knockdown improves experimental diabetic polyneuropathy independently of glycemia

Poster No:
O 531

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Introduction:
The neuropathic deficits of chronic diabetic neuropathy may be rescued by strategies supporting the intrinsic regenerative plasticity of peripheral neurons. Retinoblastoma 1 (Rb1), a tumour suppressor molecule expressed in adult sensory neurons, brakes neuron growth by binding and inhibiting divergent E2F1 transcriptional signaling. Its knockdown enhances adult neuron growth. Previous studies have shown that Rb1 knockdown improves neurite outgrowth in vitro, the outgrowth of axons following transection, and regeneration of mouse sciatic axons when applied locally, either immediately after crush injury or when applied two weeks later, once regeneration has initiated.

Methods:
Chronic models of type 1 (STZ-induced) diabetes mellitus in mice with endpoint measurements of hindpaw thermal sensation, epidermal innervation, multifiber electrophysiology. Near nerve local unilateral or intranasal siRNA administration.

Results:
Here we show, using two different approaches, that Rb1 knockdown rescues neuropathic deficits in established experimental diabetic polyneuropathy independent of glycemia. In the first strategy, we show that Rb1 mRNA in dorsal root ganglia was susceptible to knockdown by ipsilateral delivery of an siRNA coupled with electroporation in the innervated hindpaw. In chronic diabetic mice, Rb1 siRNA was associated with higher numbers of ipsilateral than contralateral epidermal axons, and improvement in thermal sensation compared to nonspecific scrambled control siRNA given to the opposite paw over only 14d of treatment. In the second strategy we applied Rb1 siRNA by intranasal administration in adult mice with chronic experimental type 1 DM over a period of one month. Rb1 siRNA was associated with improvement in both motor and sensory conduction velocity, and thermal sensation.

Conclusions:
The findings identify wider impacts of this molecular approach toward the treatment of axonal neuropathy, specifically neuropathic deficits in diabetes. The impacts rely on supporting neuron plasticity despite unchanged hyperglycemia.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: Canadian Institutes of Health Research

Keywords: diabetic polyneuropathy, Retinoblastoma1, siRNA

Neuropathic Pain Consortium (NPC) Abstracts

O 532 - 540

Molecular profiling of human epidermis in SCN9A-related painful neuropathy patients reveals unique signature

Poster No:
O 532

Authors:
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Introduction:
Painful neuropathies, although characterized by different etiologies and clinical symptoms, share the involvement of small nerve fibers and epidermal cells. The epidermis represents a complex dynamic microenvironment that controls neuron-cell crosstalk and influences nociception and pain initiation. Studies on microRNA in pain preclinical models have yielded insights into pathophysiological mechanisms, identifying nociception-related species differences and pinpointing potential drug candidates. We aimed at bridging the translational gap towards the clinic.

Methods:
Utilizing microfluidic array for unbiased microRNA and customized pain-gene array for mRNA profiling, we generated a human pain-related integrative miRNA and mRNA molecular profile of the epidermis in a deeply phenotyped cohort of patients with SCN9A-related painful neuropathy not responding to currently available therapies, and sex and age matched healthy individuals. Gene targets, biological processes and pathways were identified in silico, and associated with experimental data to construct integrative functional network. To study the impact on protein expression, we performed immunofluorescence staining against Nav1.7 in skin biopsy specimens.

Results:
We identified four miRNAs strongly discriminating patients from healthy individuals, confirming their effect on differentially expressed gene-targets driving peripheral sensory transduction, transmission modulation and post-transcriptional modification, with strong effects on gene-target NEDD4, which is known for its effect on Nav1.7 expression and neuronal growth and excitability. We identified a complex epidermal microRNA-mRNA network based on tissue-specific experimental data, supporting the hypothesis of the epidermis as a polymodal nociceptor. Immunofluorescence staining showed increased Nav1.7 signal intensity in keratinocytes in patients, that strongly inversely correlated with NEDD4 and identified miRNA expression, suggesting post-transcriptional fine tuning of pain-related protein expression.

Conclusions:
Our targeted molecular profiling advances the understanding of specific neuropathic pain signatures and may accelerate process towards personalized medicine.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: PAIN-net Project: Molecule-to-Man Pain Network, EU Research Framework Programme H2020/Marie Skłodowska-Curie Actions, grant agreement number 721841 (MA, SDH, SGW, CGF, GL) and Italian Ministry of Health (RRC).

Keywords: neuropathic pain, miRNA profiling, molecular signature, skin biopsy, channelopathy

Peripheral Pain Captured Centrally: Altered Brain Morphology On MRI In Small Fiber Neuropathy

Poster No:
O 533

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Introduction:
Pain is a hallmark symptom of small fiber neuropathy (SFN) and may have many phenotypic faces. Pain phenotypes or severity of pain in SFN may yield structural changes in the brain as observed in other chronic pain conditions, yet this remains an understudied neurobiological domain of SFN. The current study aims to characterize the brain morphological patterns of pain severity and phenotypic pain forms as reported by SFN patients with or without a gain-of-function variant involving the SCN9A gene and compare these with findings seen in healthy controls (HC).

Methods:
The Neuropathic Pain Scale (NPS) was implemented across patients with idiopathic SFN (N=20) and SCN9A-associated SFN (N=12) to capture pain phenotype and severity. T1-weighted, structural MRI imaging data was collected in all patients and HC (N=21) to (i) compare regional cortical thicknesses and subcortical volumes across study cohorts and (ii) quantify the association between severity of pain and pain quality with gray matter morphological properties.

Results:
SCN9A-associated SFN patients showed significant ($p < 0.05$, corrected) increase in cortical thickness in sensorimotor regions (paracentral lobule and precentral gyrus) compared to idiopathic SFN patients, while reduced cortical thicknesses were quantified in more functionally diverse regions (i.e., insula and anterior midcingulate, and dorsal posterior cingulate cortices). Idiopathic SFN and SCN9A-associated SFN patients demonstrated significant (Spearman's $P = 0.36$-0.55) correlation among the severity of itch (NPS-7) and thicknesses of the paracentral lobules, the pre-/post-central gyri, and anterior and posterior midcingulate cortices. No significant associations were found between regional cortical thickness and pain severity or other pain qualities than itch.

Conclusions:
In conclusion, in SCN9A-associated SFN, robust morphological alterations anchored within sensorimotor, salience, and default-mode networks are present. The association between severity of itch as it relates to neuropathic pain and sensorimotor structure provides a novel basis for further examining the neurobiological underpinning of itch sensations in SFN.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: The Prinses Beatrix Spierfonds (W.OB18-03).

Keywords: Itch, Small fiber neuropathy, SCN9A, Magnetic Resonance Imaging, Gray Matter

Examination Of Spontaneous Sensory Neuron Activity In Models Of Pain Using In Vivo Calcium Imaging

Poster No:
O 534

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Introduction:
Chronic pain is believed to be driven in part by spontaneous activity in what should otherwise be silent sensory neurons. Here, we have used a novel tool (in vivo calcium imaging) to assess activity in hundreds of sensory neurons simultaneously in two pain models: Complete Freund's adjuvant (CFA)-induced inflammation and spared nerve injury (SNI).

Methods:
Sensory neuron activity was examined using in vivo GCaMP6s calcium imaging of murine L4 dorsal root ganglion (DRG). Spontaneous activity was assessed at baseline. Afferents with intact receptive fields were identified with mechanical stimulation of the hind paw. In some experiments the nerve was electrically stimulated between the injury site and DRG, and lidocaine (2% w/v) was applied to the DRG to block activity.

Results:
One day following CFA injection, the proportion of neurons with spontaneous activity (31.5%, +/- 4.8, n=4) was significantly increased compared to control mice (10.2% +/- 1.1; n=3; p=0.01, unpaired t-test). Conversely, 3 weeks following SNI, the proportion of neurons with spontaneous activity (10.8%, +/- 1.5, n=8) was similar to control mice (9.0%, +/- 2.2, n=7; p=0.5, unpaired t-test). GCaMP fluorescence was increased in neurons of SNI mice compared to controls: specifically, the injured (ligated) afferents had fluorescent levels 2.18 (+/- 0.17) fold greater than that of intact (non-ligated) afferents. Most injured neurons (88.2% +/-0.7) increased their fluorescence in response to electrical stimulation, but their elevated levels of baseline fluorescence were not attenuated following lidocaine application to the DRG.

Conclusions:
CFA increased spontaneous activity in sensory neurons in line with what was expected from previous electrophysiological studies. In contrast, in vivo calcium imaging may not be suitable for spontaneous activity detection following SNI, since injured afferents had much higher baseline fluorescence, which was not coupled to voltage-gated sodium channel activation and therefore either caused by increased GCaMP6s expression or raised intracellular calcium ion concentrations.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: FD is the recipient of a Medical Research Foundation Prize (MRF-160-0015-ELP-DENK-C0844). FD & GG are funded by an Advanced Pain Discovery Platform UKRI MRC grant (MR/W027518/1).

Keywords: Neuropathic pain, In vivo calcium imaging, Spontaneous activity

Finding Novel Targets Linked with Neuropathic Pain in Human Lingual Nerve Neuromas Using Spatial Transcriptomics

Poster No:
O 535

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Introduction:
Lingual nerve neuromas may form following injury to the lingual nerve, which can occur during routine surgeries such as third molar removal. The formation of scar tissue between the nerve endings, coupled with Schwann cells proliferation and the presence of pro-inflammatory molecules creates a physical barrier that may impair axonal regeneration. Patients can experience symptoms including pain, altered sensation and numbness. Surgical excision of the neuroma and the reconnection of the nerve ends promotes functional recovery. The resected tissue is collected along with the clinical information, including the pain intensity reported by the patient, which enables us to classify the samples in painful and non-painful groups and identify genes dysregulated in the presence of pain. The aim of this work is to identify novel pain-relevant targets in human lingual nerve neuromas using spatial transcriptomics.

Methods:
The Visium FFPE technology enables the quantification of 17,943 transcripts from a tissue section retaining information on their spatial localization. Bulk RNA-seq and RNAscope were also employed to profile the gene expression in painful and non-painful samples. A ligand-receptor interactome analysis was performed to identify relevant targets for the development of new analgesics.

Results:
Our transcriptomic data reveal the presence of several cell types including Schwann cells, immune cells, fibroblasts and endothelial cells in the neuromas. Putative axonal transcripts (Nav1.7 and TRPV1), and leukocytes and macrophages markers (CD45, CD68) are detected in barcodes that overlay the nerve fascicles. Preliminary results indicate that HLA-A, expressed in areas containing putative TRPV1-positive axons, is upregulated in the presence of pain and potentially interacts with APLP2, expressed in trigeminal sensory neurons and shown to play a role in neuropathic pain.

Conclusions:
In summary, this work provides a detailed characterization of the transcriptional landscape of human injured peripheral nerves, contributing to the identification of novel targets for the treatment of neuropathic pain.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Neuropathic pain, Spatial transcriptomics, Nerve Injury, Trigeminal

Are Skin Fibroblasts Persistent Producers of Inflammatory Mediators of Pain in Patients with Painful Diabetic Neuropathy?

Poster No:
O 536

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Introduction:
Peripheral neuropathy is a common neurological complication of diabetes, and about half of the patients develop neuropathic pain. Available therapies for neuropathic pain, including antidepressants and antiepileptic drugs, sometimes induce many undesirable side effects and provide partial relief only in a subpopulation of patients. Here, we propose that targeting peripheral source of inflammatory mediators of pain in the skin, may promote a homeostatic metabolic milieu that disrupts the inflammatory cascade and relief pain. Fibroblasts, as one of the main skin cell populations, are in intensive interaction with nerves and nociceptors. Therefore, skin fibroblasts collected at the site of pain are an interesting cell model to study peripheral pain sensitization in patients with painful diabetic neuropathy.

Methods:
We have established a biobank of skin fibroblast from 18 skin biopsies from deeply phenotyped patients, divided into 4 groups: healthy controls, patients with diabetes without neuropathy, and patients with diabetes with neuropathy with and without neuropathic pain. We have performed a pilot study on two healthy controls and two pain patients using ELISA, to measure the excretion of the pain-related mediator interleukin-6 by skin fibroblasts, with or without stimulation by TNF-α.

Results:
Our results show that skin fibroblasts from diabetic neuropathic pain patients, but not controls, have become persistent producers of interleukin-6, even in the absence of inflammatory mediators such as TNF-α.

Conclusions:
The production of IL-6 by fibroblasts derived from patients with diabetic neuropathic pain could be due to a long-term metabolic stress and epigenetic remodeling caused by diabetes. This might provide a new perspective in understanding peripheral neuropathic pain. To confirm and further explore the inflammatory properties of the fibroblasts, we will analyze all patient and control fibroblast samples using an 8-plex cytokine profile and Luminex Technology.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Painful Diabetic Neuropathy, Fibroblasts, Mitochondria, Inflammation

Uncovering PDN-induced cutaneous nerve degeneration through an unbiased single-cell transcriptional approach

Poster No:
O 537

Authors:
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Introduction:
Painful diabetic neuropathy (PDN) is one of the most common and intractable complications of diabetes. PDN is characterized by small-fiber degeneration, which can progress to complete loss of cutaneous innervation and is accompanied by neuropathic pain. Uncovering the mechanisms underlying the degeneration of cutaneous nerves in PDN remains a major challenge to finding effective and disease-modifying therapy. Sensory nerve afferents normally extend into the epidermis in close communication with keratinocytes, but degenerate in diabetic skin. Understanding how keratinocytes communicate with cutaneous afferents and how this communication affects axonal degeneration in PDN may contribute to gaining novel insights into this condition.

Methods:
We used a mouse model of PDN where mice were fed a regular diet (RD,11% fat) or a high-fat diet (HFD,42% fat) for 10-weeks developing glucose intolerance, mechanical allodynia, and small fiber neuropathy. Using an unbiased single-cell sequencing approach, we captured keratinocyte gene expression profiles from mouse paw skin and from PDN-patients skin biopsy to explore the mechanisms by which keratinocytes communicate with cutaneous afferents and how this communication impacts axonal degeneration underlying neuropathic pain in PDN.

Results:
scRNA-seq from RD and HFD mice and PDN-patients identified several differentially expressed genes, showing a transcriptional profiling map of two skin cell populations, immune cells and keratinocytes at different stages of differentiation. In addition, by comparing the transcriptomes from skin of PDN patients to those of HFD mice, we have identified genes putatively expressed in both human and mouse skin.

Conclusions:
By single-cell transcriptomics which currently represents the most impactful method to characterize cell populations in a given tissue, we have improved the understanding of neuron-keratinocyte communication in diabetic skin. Our results could be translated into new topical interventions, including those based on GPCR agonism or antagonism, which could meet the unmet need for therapy for both small-fiber degeneration and neuropathic pain in diabetes.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Painful diabetic neuropathy, Neuropathic pain, Keratinocytes, Peripheral Neuropathy

A Human In-vivo Model of Cutaneous Glioneural Plasticity: Preliminary Histological and Psychophysical Data

Poster No:
O 538

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Introduction:
The purpose of this study is to track histological changes in cutaneous nerve fiber and Schwann cell density and somatosensation in a human model of high-dose (8%) capsaicin-ablation.

Methods:
In two pilot experiments, a skin area on the ventral thigh was exposed to 8% capsaicin patches for 24h. Skin punch biopsies were taken at baseline, 24h, 9 and 17 days after patch removal. Intraepidermal nerve fiber density (IENFD), and Schwann cell epidermal projections and dermal somata were quantified based on immunohistochemical stainings (PGP9.5/S100/Sox10/DAPI). Responses to suprathreshold heat stimuli on a numerical rating scale, and mechanical pain thresholds (MPT) were assessed at each timepoint.

Results:
24h-capsaicin exposure led to a profound (>95%) and progressive loss of IENFD over time. There was immunohistochemical evidence of increased dermal fiber density, Schwann cell soma and projection densities at day 9. At day 17 both Schwann cell somata and epidermal projections showed a loss. These histological findings were paralleled by a complete loss of heat pain sensation, and 2 to 3-fold increases in MPTs at all timepoints compared to baseline.

Conclusions:
Loss of IENFD seems to precede loss of Schwann cells, and – as part of an ongoing larger study – the trajectory of glioneural regeneration is being explored at later timepoints postpatch removal. A transient increase in Schwann cell and dermal fiber densities indicates potential but unsuccessful compensatory mechanisms, which is currently being replicated in a larger cohort. The implications of this study are manifold. Studying cutaneous structure-function associations with the capsaicin-ablation model may provide novel insights into the pathophysiology of (painful) peripheral neuropathies. Moreover, novel biomarkers for the prediction of the therapeutic response of capsaicin can be explored and cutaneous glioneural regenerative capacity within the peripheral nervous system may be investigated. Results of the larger cohort study will be presented at the meeting.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Schwann cell, Small Fiber, Capsaicin, Histology

The Nociceptive Activity of Peripheral Sensory Neurons is Modulated by the Neuronal Membrane Proteasome

Poster No:
O 539

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Introduction:
The proteasome is critical for peripheral nervous system (PNS) function through mechanisms that remain largely unknown. Here, we investigated proteasomes in the mammalian PNS and revealed the neuronal membrane proteasome (NMP), originally discovered in the central nervous system, on the somata and proximal and distal axons of peripheral sensory neurons and investigated its role in modulating PNS function.

Methods:
Using immuno-electron microscopy, surface protein biotinylation and purification, and antibody feeding approaches we revealed the presence of the NMP in PNS sensory neurons. We used an NMP-specific membrane-impermeable inhibitor and classical behavioral approaches to investigate the function of the NMP in-vivo. Moreover, we used Calcium imaging experiments to further investigate the function of the NMP in cultured neurons.

Results:
We determined that specific inhibition of the NMP on distal nerve fibers innervating the mouse hind paw led to an acute reduction in behavioral mechanosensitivity, but no change in heat sensitivity. Investigating the mechanisms of these findings, our experiments show that NMPs are enriched on a subset of sensory neurons that include nonpeptidergic nociceptors, which are known to participate in mechanosensory behavior, but is not found on glial cells. Consistent with a role in regulating nociceptor function, PNS NMP inhibition reduced Ca2+ signaling via the nociceptive neuron-specific P2X3 purinoreceptor.

Conclusions:
Taken together, our findings identify in the PNS cell-specific expression of spatially separated NMPs that have an ongoing role in modulating sensory signaling processes, including mechanosensory behavior. These observations provide critical insight into understanding proteasome function in the PNS and potentially identify the NMP as a new target for pain regulation.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: NIH-NIGMS NRSA F32NS119202 and Merkin Peripheral Neuropathy and Nerve Regeneration Center grant 22DF-C1/232 to EVL

Keywords: Proteasome, Sensory neurons, neuronal membrane proteasome, Mechanosensory, Pain

Eplontersen in Hereditary ATTR-polyneuropathy: Week 66 Final Analysis of the Phase 3 NEURO-TTRansform Study

Poster No:
O 540

Authors:
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Introduction:
Hereditary transthyretin amyloidosis with polyneuropathy (ATTRv-PN) is a rare, progressive, and debilitating disease caused by accumulation of amyloid fibrils composed of transthyretin (TTR) protein in multiple organ systems. Eplontersen, a ligand-conjugated antisense oligonucleotide that inhibits TTR protein synthesis, is being assessed in the ongoing, phase 3, international, open-label NEURO-TTRansform study (NCT04136184). Previously reported data established that both coprimary endpoints and the key secondary endpoint were met at the prespecified Week 35 interim analysis. Specifically, eplontersen treatment resulted in significant reductions in serum TTR concentration and neuropathy impairment, as well as improved patient quality of life, compared with external placebo (from the NEURO-TTR study [NCT01737398]). Eplontersen treatment also demonstrated an acceptable safety and tolerability profile. Here we evaluate the efficacy and safety of eplontersen at Week 66 in patients with ATTRv-PN in the NEURO-TTRansform study.

Methods:
NEURO-TTRansform enrolled 168 adults with ATTRv-PN, defined by Coutinho Stage 1–2, a documented TTR sequence variant, and signs/symptoms consistent with polyneuropathy (Neuropathy Impairment Score [NIS] ≥10 and ≤130). Patients were assigned 6:1 to eplontersen 45 mg subcutaneously every 4 weeks (n=144) or inotersen 300 mg once weekly (n=24) until the prespecified Week 35 interim analysis, after which all patients received eplontersen 45 mg subcutaneously every 4 weeks. Patients in

the eplontersen group were compared with an external placebo group from the NEURO-TTR study. Coprimary efficacy assessments at Week 66 included serum TTR concentration, modified NIS +7, and the Norfolk Quality of Life-Diabetic Neuropathy score. Safety and tolerability were also assessed.

Results:
Efficacy and safety results from the Week 66 final analysis will be presented.

Conclusions:
Results from the Week 66 final analysis will provide longer-term data on the efficacy and safety of eplontersen in patients with Stage 1 or 2 ATTRv-PN.

References:
No

References 1:

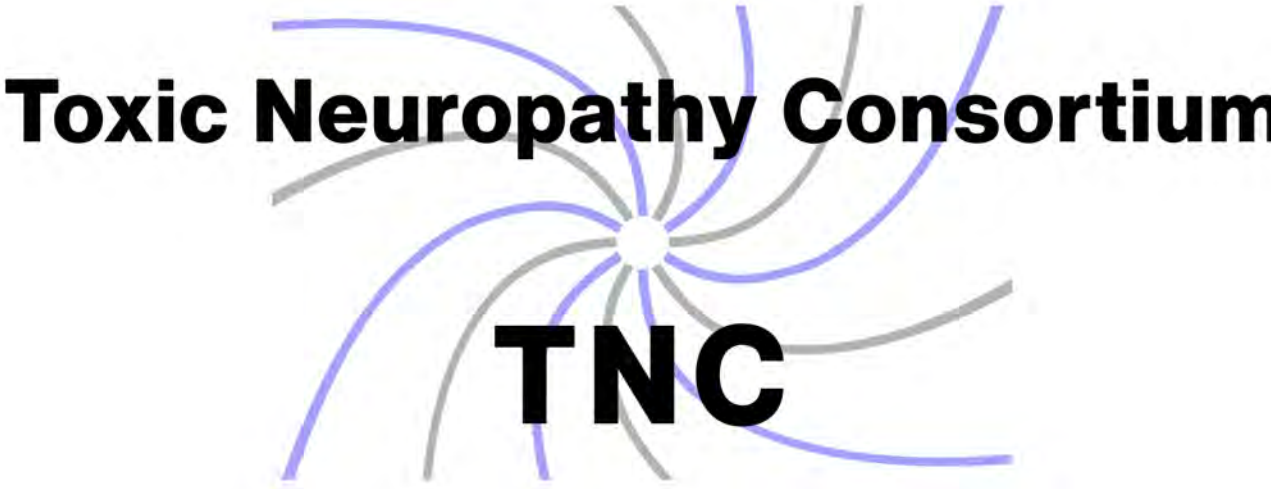
References 2:

References 3:

References 4:

Grant Support: This study was funded by Ionis Pharmaceuticals, Inc.

Keywords: hereditary transthyretin amyloidosis, polyneuropathy, efficacy, safety, quality of life



Toxic Neuropathy Consortium (TNC) Abstracts

O 541 - 549

Chemotherapy-Induced Peripheral Neurotoxicity: why should we care?

Poster No:
O 541

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Introduction:
Chemotherapy Induced Peripheral Neurotoxicity (CIPN) causes sensory loss and neuropathic pain at limb extremities. It can have a negative impact on working abilities due to emerging disabilities (e.g., sensory ataxia). CIPN socio-economic burden was not extensively investigated so far: we are exploring this matter in a retrospective/prospective study.

Methods:
There are 2 working packages (WP). In WP1 we are enrolling CIPN patients to accurately detect and grade CIPN, matching this condition with socio-economic assessments. In WP2 we analysed a large, general administrative database from Regione Lombardia (data from all adult citizens in the 2000-2021 period).

Results:
We have enrolled 25 patients in WP1 with a grade 1-2 CIPN (as assed via Total Neuropathy Score) and we have collected socio-economic patient-level information. In WP2 we estimated the incidence of CIPN in the population of patients affected by cancer. Given that CIPN is not officially labelled in this administrative database, we used information about medical treatments to indirectly detect CIPN. To avoid confounding factors, we considered only patients affected by cancer and without other comorbidities potentially leading to neuropathy. WP2 results showed that, among the 2 millions patients treated for cancer in 2019, 52 thousands did not present other comorbidities leading to neuropathy (mean age: 61 y.o.; 46% male). The public health expenditure to treat them was about 960 euro/person. Of them, 23% received CIPN-related medical treatments which account for 5% of the total expense.

Conclusions:
Our aim is to learn more about the socio-economic cost of CIPN. It is important that this condition is formally classified on medical records, with all the ensuing consequences, given the potential detrimental effect on the quality of life of affected people. Given our preliminary results, it is of highly relevance to accurately define CIPN socio-economic burden to plan future health care programs. We are extending WP1 in a large international multicenter study.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: This work was supported by Bicocca Starting Grant.

Keywords: CIPN, health economics, chemotherapy induced peripheral neuropathy, chemotherapy induced peripheral neurotoxicity, cancer survivors

Wlds prevents axon degeneration in three different mouse models of Chemotherapy Induced Peripheral Neuropathy

Poster No:
O 542

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Introduction:
Chemotherapy-induced peripheral neuropathy (CIPN) is a debilitating side effect caused by anticancer drugs that results in dose reduction or discontinuation of chemotherapy. Distal axon degeneration seen in CIPN shares molecular pathways with Wallerian degeneration. The Wlds (Wallerian degeneration slow) mutation results in axonal expression of a fusion protein containing NAD synthesizing enzyme NMNAT1 (Nicotinamide mononucleotide adenylyltransferase 1) delays the onset of Wallerian degeneration in axons and provides insight to the mechanisms of axonal degeneration caused by various insults.

Methods:
Paclitaxel, Cisplatin and Bortezomib were administered by tail vein injections to Wlds and wild-type mice. Baseline nerve conduction studies and thermal sensitivity tests were carried before the start of the injections and endpoint tests were done after onset of the peripheral neuropathy. Mice were euthanized and tissues were harvested for histopathological evaluation.

Results:
The key manifestations of peripheral neuropathy in these CIPN models, including direct axonal loss at the distal terminals, pain hyper- or hypo-sensitivity, and electrophysiological abnormalities, were observed in wild-type mice, but not in Wlds mice.

Conclusions:
These results confirm the previous data with paclitaxel in Wlds mice and extend it to cisplatin and bortezomib and affirms the key role NMNAT plays in distal axonal degeneration.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: CIPN, Mouse models of CIPN, Wallerian degeneration, Wlds, NMNAT

Angiotensin type 2 receptor, a new target, to prevent chemotherapy induced peripheral neuropathy

Poster No:
O 543

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Institutions:
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Introduction:
Chemotherapy Induced Peripheral Neuropathy (CIPN) is a frequent adverse event, and affects 30% to 90% of treated patients. There is no effective and specific preventive treatment. Renin Angiotensin System (RAS) elements [angiotensin 1 converting enzyme (ACE), angiotensin 2 receptors: AT1 and AT2] are expressed in the peripheral sensory nervous system and have a role in neuroprotection/pain modulation. We studied the effects of RAS modulators on mice models of peripheral neuropathies induced by the 2 most neurotoxic antimitotic agents: vincristine (VCR), paclitaxel (PTX).

Methods:
VCR was injected each day during 7 days (100 µg/kg/d; ip). PTX was injected 4 times during 8 days (6 mg/kg/2 days; ip). Neuropathy functional assessment (motor coordination, tactile sensitivity, heat nociception) was performed before chemotherapy, during and after chemotherapy. Paw skin, sciatic nerve, DRG collection was performed at the day of the maximum of functional neuropathy for a morphological analysis and immunohistology studies. RAS treatments: candesartan (AT1R antagonist), ramipril (ACE inhibitor), C21 (AT1 receptor agonist) and PD123319 (antagonist AT2), was administered (ip) one day before and during chemotherapy.

Results:
VCR and PTX induced no modification on motor performance and heat nociception. Both induced a mechanical allodynia with a decrease of intraepidermal nerve fibers (IENF) and dorsal root ganglia (DRG) neuron densities. Moreover, both drugs decreased nerve fibers numbers in the sciatic nerve. Candesartan and ramipril alleviated sensory neuron loss, both in VCR and PTX mice. Candesartan and C21 protected tactile sensitivity in VCR mice (disappearing effect with PD123319). Ramipril alleviated a loss of normal tactile sensitivity in PTX mice (disappearing effect with PD123319). AT2R-neuroprotective effect of candesartan and ramipril was confirmed in AT2R KO mice.

Conclusions:
Neuroprotective effect of candesartan and ramipril is specifically mediated by AT2R in CIPN, a new target to explore in clinical trial.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: peripheral neuropathy induced by Chemotherapy, vincrsitine, paclitaxel, Renin angiotensin system, Angiotensin 2 receptor

Glia Neuro-Immune Interaction in Dorsal Root Ganglia in a Mouse Model of Bortezomib-Induced Neuropathy

Poster No:
O 544

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Introduction:
Chemotherapy-induced neuropathy is the main dose-limiting side effect of bortezomib (BTZ), a chemotherapeutic widely used to treat multiple myeloma and amyloidosis. We demonstrated recently that while some chemotherapeutics exert direct toxic effects on axons, BTZ leads to axon degeneration via signals from neuronal somata, which are in the dorsal root ganglia (DRG). However, what these signals are and how they arise is unknown.

Methods:
To address this question, we treated mice intravenously with BTZ twice weekly for 8 weeks and determined the impact on peripheral nerves and DRGs.

Results:
We observed a loss of myelinated axons in the sural nerve, decreased compound nerve action potential amplitude of the tail nerve, impaired rotarod performance, increased fatigue and a mild decrease of intra-epidermal nerve fiber density, closely mirroring the neuropathy seen in humans. In DRGs, a subset of neurons was surrounded by hypertrophied satellite glia cells (SGC). SGC are unique in that they completely envelope each sensory neuron soma, allowing for close bidirectional communication. Staining with glial fibrillary acidic protein (GFAP), a marker of SGC activation, revealed that the number of neurons surrounded by activated SGC increased dramatically following BTZ. Interestingly, GFAP+ SGC enveloped a subset of large (NF200+) and small non-peptidergic (IB4+) neurons, but not peptidergic (CGRP+) nociceptors, suggesting that BTZ-induced SGC activation affects specific DRG neuron subtypes. scRNA seq analysis revealed that BTZ induces in SGC upregulation of genes enriched in phagocytosis and immune-responses. In line with immune activation in DRG following BTZ, we found increased numbers of macrophages, which express genes involved in B and T-cell activation.

Conclusions:
Thus, we show that BTZ induces changes in the DRG sensory neuron microenvironment that differentially affects specific neuron types and suggest that manipulating non-neuronal cells may lead to new avenues to treat BTZ-induced neuropathy

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: Hope Center of Washington University pilot program, R01 CA267905-01

Keywords: chemotherapy-induced neuropathy, DRG, satellite glia cells, immune, bortezomib

Neuron-Macrophage Interactions in Models of Chemotherapy-Induced Peripheral Neuropathy

Poster No:
O 545

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Introduction:
Chemotherapy-induced peripheral neuropathy (CIPN) is a chronic and painful condition that affects over 3 million people in the US alone. Despite the prevalence, there is no effective clinical intervention, and the underlying pathological mechanisms are poorly understood. Previous studies have shown that CIPN pathology can often accompany pro-inflammatory changes. To better understand this immune response and its involvement in CIPN, we have focused on investigating the peripheral interactions between macrophages and nociceptive nerve terminals using Drosophila and mouse CIPN models.

Methods:
Leveraging a previously established Drosophila CIPN model (Shin et al., 2021), we aim to investigate the paclitaxel- and bortezomib-mediated transition of macrophages through different pathological stages of neurodegeneration. Using transcription reporters, we quantified the transition of macrophages at a single-cell level and spatially mapped these cells in relation to nociceptive neuron terminals in vivo. To molecularly characterize macrophages, we performed transcriptional analyses of candidate immune pathway genes. To further decipher how macrophage transitions contribute to CIPN pathology, we investigated several genes previously characterized for macrophage localization, transition, and modulation. Finally, in vitro mouse macrophage-neuron experiments are in progress to validate mechanisms mediating neuron-immune interactions.

Results:
Both paclitaxel and bortezomib increased the proliferation of resident macrophages in the early pathological stage but induced different macrophage transitions at later stages. Furthermore, qRT-PCR results showed an upregulation of distinct immune pathway markers that revealed pathological stage-dependent states of macrophages. Finally, our preliminary results from mouse macrophages suggest modulating macrophages may reduce toxicity associated with chemotherapeutic treatment.

Conclusions:
Our study shows chemotherapy-induced changes in macrophages that correspond to neuronal pathology in CIPN. This includes proliferation, immune pathway activation, and molecular changes of these macrophages throughout CIPN pathogenesis. Our result is expected to contribute to a better understanding of the molecular mechanisms underlying CIPN and allow for targeted modulation of the immune system to prevent and treat sensory neuropathy.

References:
Yes

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Shin, G.J.-e., M.E. Pero, L.A. Hammond, A. Burgos, A. Kumar, S.E. Galindo, T. Lucas, F. Bartolini, and W.B. Grueber. 2021. Integrins protect sensory neurons in models of paclitaxel-induced peripheral sensory neuropathy. Proc. Natl. Acad. Sci. USA.

References 2:

References 3:

References 4:

Grant Support: NCI, 1R21CA274588-01

Keywords: CIPN, macrophages, inflammatory, machine learning, Drosophila

Clinical Factors Associated With Improvement In Chemotherapy-Induced Peripheral Neurotoxicity

Poster No:
O 546

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Introduction:
Chemotherapy-induced peripheral neurotoxicity (CIPN) is a common adverse effect of numerous anti-cancer treatments with symptoms often persisting post treatment completion. However, there is considerable variability in CIPN recovery, and little is known about clinical profiles of patients who experience CIPN symptom improvement. This longitudinal study aimed to identify clinical phenotypes associated with improvement in CIPN.

Methods:
Patients commencing neurotoxic treatments (taxane, platinum, vinca-alkaloid, bortezomib, thalidomide) were assessed longitudinally. Data from two timepoints were compared, end-of-treatment and 6-12 months post treatment. CIPN was graded by the National Cancer Institute (NCI) sensory neuropathy scale by trained researchers after comprehensive evaluation. Improvement in CIPN was defined as reduction by at least one NCI grade. Odds ratios (OR) were computed using logistic regression with results presented as mean±SD.

Results:
270 patients (54.9±12.5 years, 68.1% female) were included in the study, with 207 (76.7%) patients experiencing CIPN by end-of-treatment. At second follow-up (months=6.9±2.6), 101(48.8%) experienced CIPN improvement. Each year of older age was associated with a 3.8% decrease in the odds of CIPN improvement ($P<0.005$), while there was no significant association with other factors (gender, body mass index, diabetic status, baseline PN, all $P>0.05$). There was no difference in CIPN improvement between patients receiving taxane compared to platinum therapy ($P>0.05$), or between patients receiving paclitaxel versus paclitaxel with carboplatin ($P>0.05$). Similarly, subgroup analysis in taxane-treated patients with CIPN by end-of-treatment (n=130) suggested age was associated with decrease in CIPN improvement ($P<0.001$), but not gender, BMI, diabetic status, baseline PN or paclitaxel dose (all $P>0.05$).

Conclusions:
This series of longitudinal analyses demonstrated CIPN as a long-term toxicity with only 49% of patients experiencing symptom improvement at 6-12 months post treatment. Older age may be a risk factor for CIPN persistence but mechanisms underlying CIPN improvement remain complex, with genetic risk factors likely important in CIPN symptom reversibility.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Chemotherapy-induced peripheral neurotoxicity, symptom improvement, clinical risk factors, longitudinal study

The NAD Consuming Enzyme SARM1 Drives Neurodegeneration Caused By Environmental Neurotoxins And Vitamin B6.

Poster No:
O 547

Authors:
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Institutions:
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Introduction:
SARM1 is a key regulator of programmed axon death, a well-characterized pathway leading to axon degeneration. SARM1 is a multi-functional enzyme that consumes NAD and NADP, with dramatic consequences for neuron energy metabolism. Accumulating evidence in both pre-clinical disease models and in human disease suggests that programmed axon death contributes to neurodegeneration in humans, including in toxic neuropathies, ALS, and polyneuropathies. We have recently shown that vacor, a disused rodenticide and lethal neurotoxin in humans, activates SARM1, which in turn mediates axon death and neurodegeneration both in vitro and in vivo in mice.

Methods:
We used mouse primary neuronal cultures and axon degeneration assays to evaluate the role of SARM1 in response to structurally similar environmental neurotoxins.

Results:
Here, we identify additional molecules causing SARM1-dependent axon degeneration, including 3-acetylpyridine (3AP), previously used as an additive in tobacco products and flavoring agents, and the glycolysis-inhibitor 6-aminonicotinamide (6AN). The molecular structures of Vacor, 3AP and 6AN include a pyridine ring, a moiety that is frequently found in drugs and pesticides. This raises the question of whether other pyridines could cause SARM1-dependent neurotoxicity. Pyridoxine (vitamin B6) contains a pyridine ring as its core. Notably, high doses of pyridoxine cause peripheral neuropathy in humans, but the pathogenic mechanism underlying its toxicity remains unclear. Here we show that pyridoxine causes SARM1-dependent axon degeneration and cell death, as both genetic deletion and knockdown of SARM1 rescue neurotoxicity caused by pyridoxine in vitro.

Conclusions:
These findings suggest that SARM1 mediates environmental neurotoxicity and contributes to toxic neuropathies, raising the question of whether other environmental chemicals or structurally similar drugs in use today also activate programmed axon death, and contribute to disease. Investigating the structural and functional properties of SARM1 activators will further improve our understanding of SARM1 regulation, and the specific functions responsible for its pro-neurodegenerative role.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: E.M. is funded by the Cambridge Trust; A.L. is funded by the Wellcome Trust (grant number 210904/Z/18/Z).

Keywords: SARM1 , axon degeneration , toxic neuropathy , pyridoxine

Paclitaxel neurotoxicity is mediated by Eg5 dependent X-ROS formation in epidermal keratinocytes

Poster No:
O 548

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Introduction:
Stabilized microtubules have been associated with various pathological conditions, including chemotherapy-induced peripheral neuropathy. The underlying mechanisms are still poorly understood. We previously identified a new, epidermis-specific function for MMP-13 in paclitaxel neurotoxicity and demonstrated that paclitaxel treatment induces hydrogen peroxide (H2O2) formation leading to MMP-13 dependent extracellular matrix degradation and the degeneration of cutaneous unmyelinated axons.

Methods:
Here we analyzed upstream mechanisms leading to paclitaxel-induced H2O2 formation using zebrafish and mouse models, and patient skin to identify relevant mechanisms.

Results:
These studies reveal a previously unknown role for Kinesin 5 (Eg5) as a target of paclitaxel leading to keratinocyte-specific aggregation of detyrosinated microtubules and nuclear activation of NADPH oxidase 1 (Nox1) via altered mechanotransduction of microtubules that impacts nuclear shape. We further show that knockout of Eg5 prevents Taxol-induced axon degeneration whereas Eg5 overexpression in epidermal keratinocytes is sufficient to induce degeneration. We also determined that CIPN patient skin shows significant molecular changes in the epidermis, consistent with these findings.

Conclusions:
Our research demonstrates Eg5 as previously unknown target of paclitaxel upstream of microtubule aggregation and axon degeneration.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: NIH R01CA215973-05

Keywords: CIPN, unmyelinated sensory neurons, paclitaxel, epidermis, Eg5

Development of an innervated skin on a chip model to study neurovascular interactions

Poster No:
O 549

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Introduction:
Neurovascular interactions have been shown to play a pivotal role in skin repair and regeneration, as evidenced by the delayed healing of denervated skin. The generation of a vascularized skin including a properly differentiated epidermis as well as functional innervation and vasculature still represents a major challenge. The purpose of this work is to develop an innovative, fully human, skin-on-a chip enabling the investigation of cutaneous innervation on skin pathophysiology.

Methods:
Cell sourcing: human induced pluripotent stem cells (Phenocell) were differentiated into sensory neurons (iSN) and Schwann cells (iSC) according to established protocols. Human dermal microvascular endothelial cells (HDMECs) and fibroblasts were isolated from human surgical waste with regulatory approval. Chips: in house microfluidic chips were electrostatically attached over glass coverslips previously coated with Poly-D-Lysine and laminin. HDMECs and fibroblasts were seeded in the lateral compartments while iSN and iSC were seeded in the central compartment and maintained in culture until neuronal extensions reached the endothelial compartment. Mono and co-cultures were also assessed on a commercial chip (BeOnChip®)

Results:
iSN expressed expected neuronal markers (i.e. NF 200, β3-tubulin, TRPV1 and TrkA), exhibited spontaneous firing and released Substance P by day 16. iSC expressed S100, GFAP and GAP43. HDMECs and FHN expressed CD31 and CD90, respectively and co-culture showed the elaboration of a pseudo vascular network. From both microfluidic chips and conditioned media from iSN applied to endothelial cell cultures, we could observe the effect of the neural actors on the morphological organization of the endothelial compartment.

Conclusions:
Initial data present sensory neuron and Schwann cell models and their effect on endothelial cell morphology. We expect that our vascular and neural networks models could promote a better understanding of their interactions in skin pathophysiology.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: organ-on-chip, skin regeneration, sensory neurons, innervation, topical treatment

Inflammatory Neuropathy Consortium

Inflammatory Neuropathy Consortium (INC) Abstracts

O 550 - 556

Super-resolution imaging resolves ultrastructural protein pathology at the node of Ranvier in patients with polyneuropathy

Poster No:
O 550

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Introduction:
The node of Ranvier is the key element in saltatory conduction along myelinated axons. Recently, the use of new super resolution techniques allowed to reveal a 190 nm periodic arrangement of both axonal scaffold proteins and cell adhesion proteins at the node of Ranvier in mice. Yet, these ultrastructural protein arrangements remain elusive in humans, especially under pathological conditions.

Methods:
To explore new means in the ultrastructural analysis of peripheral nerve pathology, especially at the node of Ranvier, we implemented the super resolution microscopy method 'direct Stochastic Optical Reconstruction Microscopy' (dSTORM) on n = 17 nerve biopsies of patients with polyneuropathies of different etiologies and supported our data by three-color high-content confocal microscopy combined with deep learning-based analysis.

Results:
As a result, we showed that dSTORM can resolve the periodic protein arrangement in humans. The 190 nm periodicity of axonal cytoskeletal ß-II spectrin was conserved in humans at the internode, but impaired at the paranode in patients with polyneuropathy. In parallel, the periodic protein distances of the paranodal axoglial adhesion molecules Caspr-1 and neurofascin-155 were severely disturbed, with a mid- to lateral increase in periodic spacings. Colocalization analysis revealed a detachment of the axoglial proteins from axonal ß-II spectrin and a partial loss of the axoglial complex in single nodes from patients with severe polyneuropathy. High content analysis showed that a disorganization and elongation of paranodal adhesion proteins occurred especially in acute and severe axonal neuropathy.

Conclusions:
We were able to confirm the node of Ranvier as an Achilles' heel for cytoskeletal damage on an ultrastructural protein level and pinpoint its link to axoglial detachment and paranodal elongation. Super resolution microscopy was able to quantify ultrastructural changes in diagnostic samples of single patients, introducing the method as a future tool for pathophysiological studies using larger and homogenous cohorts and distinct applications.

References:
Yes

References 1:

The work described in this study has been uploaded as a preprint on medrxiv: Super-resolution imaging pinpoints ultrastructural changes at the node of Ranvier in patients with polyneuropathy Luise Appeltshauser, Janis Linke, Hannah S. Heil, Christine Kar

References 2:
An abstract with related, but not identical preliminary results has been presented by Janis Linke at the EAN 2022 meeting: https://www.ean.org/fileadmin/user_upload/ean/congress-2022/EAN2022AbstractBook.pdf

References 3:

References 4:

Grant Support: The study was supported by a grant of the Interdisciplinary Center of Clinical Research (IZKF) of the Medical Faculty of Würzburg to K.D. and K.G.H (F-N-439)

Keywords: Node of Ranvier, super respolution microscopy, dSTORM, axoglial complex, axonal polyneuropathy

A 21-bp deletion in the CD55 promotor region is associated with multifocal motor neuropathy and its disease course

Poster No:
O 551

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Institutions:
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Introduction:
To further substantiate the role of antibody-mediated complement activation in MMN immunopathology, we investigated the distribution of promotor polymorphisms of genes encoding the membrane-bound complement regulators CD46, CD55 and CD59 in patients with MMN and controls, and evaluated their association with disease course

Methods:
We used Sanger sequencing to genotype five common polymorphisms in the promotor regions of CD46, CD55 and CD59 in 133 patients with MMN and 380 controls. We correlated each polymorphism to clinical parameters.

Results:
The genotype frequencies of rs28371582, a 21-bp deletion in the CD55 promotor region, were altered in patients with MMN as compared to controls (p 0.009; Del/Del genotype 16.8% vs. 7.7%, p 0.005, OR 2.43 (1.27–4.58)), and patients carrying this deletion had a more favorable disease course (mean difference 0.26 MRC points/year (95% CI 0.040–0.490), p 0.019)). The presence of CD59 rs141385724 was associated with less severe pre-diagnostic disease course (mean difference 0.940 MRC point/year (95% CI 0.083-1.80, p 0.032)).

Conclusions:
MMN susceptibility is associated with a 21-bp deletion in the CD55 promotor region (rs2871582), which is associated with lower CD55 expression. Patients carrying this deletion may have a more favorable long-term disease outcome. These results indicate the importance of the pre-C5 level of the complement cascade in the inflammatory processes underlying MMN.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Multifocal motor neuropathy, Complement systeem, Complement regulators, Genetics

Hyaluronidase-Facilitated Subcutaneous Immunoglobulin 10% for Maintenance Treatment of Chronic Inflammatory Demyelinating Polyradiculoneuropathy

Poster No:
O 552

Authors:
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Institutions:
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Introduction:
HYQVIA/HyQvia, a facilitated subcutaneous immunoglobulin (fSCIG; human immunoglobulin G 10% with recombinant human hyaluronidase), enables high-volume immunoglobulin administration (≤600 mL/site) into subcutaneous tissue, thus reducing the required number of infusion sites and needlesticks, as well as infusion time and frequency. ADVANCE-CIDP 1 evaluated the efficacy and safety of fSCIG in preventing relapse in chronic inflammatory demyelinating polyradiculoneuropathy (CIDP).

Methods:
ADVANCE-CIDP 1 was a phase 3, randomized, double-blind trial (NCT02549170). Eligible adults (with definite or probable CIDP, Inflammatory Neuropathy Cause and Treatment [INCAT] disability scores of 0–7 and receiving stable intravenous immunoglobulin [IVIG] doses for ≥12 weeks) were randomized to fSCIG or placebo for 6 months or until relapse/discontinuation. fSCIG was administered at the same dose and interval (maximum 4-weekly) as pre-randomization IVIG. The primary outcome was the proportion of patients experiencing CIDP relapse (≥1-point increase in adjusted INCAT score from pre-study baseline) in the modified intention-to-treat population. Secondary outcomes included time-to-relapse and safety endpoints.

Results:
Overall, 132 patients (mean age 54.4 years, 56.1% male) were randomized to fSCIG (n=62) or placebo (n=70). fSCIG reduced CIDP relapse versus placebo (n=6 [9.7%; 95% CI: 4.5, 19.6] vs n=22 [31.4%; 21.8, 43.0), respectively; absolute difference: −21.8% [−34.5, −7.9], p=0.0045). Time-to-relapse was longer with fSCIG than placebo (p=0.002). While adverse events (AEs) were more frequent with fSCIG (79.0% of patients) than placebo (57.1%), severe (1.6% vs 8.6%) and serious AEs (3.2% vs 7.1%) were less common with fSCIG. The most common AEs with fSCIG were headache (n=8 [12.9% of patients]), injection site erythema (n=7 [11.3%]) and pyrexia (n=7 [11.3%]).

Conclusions:

fSCIG, administered at the same dose and interval as previous IVIG regimens, was more effective than placebo in preventing disease relapse with a favorable safety profile, supporting its potential use as maintenance CIDP treatment. Study funder/writing support funder: Takeda Development Center Americas, Inc./Takeda Pharmaceuticals International AG.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: Study funder/writing support funder: Takeda Development Center Americas, Inc./Takeda Pharmaceuticals International AG.

Keywords: Chronic inflammatory demyelinating polyradiculoneuropathy/CIDP, Facilitated subcutaneous immunoglobulin, Maintenance treatment, Phase III trial, Randomized controlled trial

Membrane proteome-wide screening of autoantibodies in Chronic Inflammatory Demyelinating Polyradiculoneuropathy using human cell microarray technology

Poster No:
O 553

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Introduction:
Clinically relevant autoantibodies are detected in only 5-10% of patients fulfilling chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) criteria. Our study assessed a human cell protein microarray technology (Retrogenix) as a novel autoantibody discovery tool in CIDP.

Methods:
Twelve CIDP serum samples (4 with known antigens, 4 with unknown antigens and IgG reactivity against neural structures and 4 typical CIDP patients) were screened for the presence of IgG autoantibodies using the cell microarray, consisting of HEK293 cells expressing >5000 human cell membrane or secreted proteins. Identified autoantibodies were subsequently validated by cell-based assays, ELISA and/or tissue immunohistochemistry, and analysed in a cohort of CIDP (n=99) and control (n=100) samples.

Results:
Serum anti-contactin-1 and anti-neurofascin-155 antibodies from patients with known antigenic reactivities were detected by the human cell microarray technology; anti-pan-neurofascin and anti-CASPR1 antibodies were not detected. Nine other relevant reactivities were found; and confirmation was possible in six of them: Ephrin type-A receptor 7 (EPHA7), potassium-transporting ATPase alpha chain 1 and subunit beta (ATP4A/4B), leukemia inhibitor factor (LIF) and interferon lambda 1, 2 and 3 (IFNL1, IFNL2 and IFNL3). Anti-EPHA7 and anti-ATP4A/4B were found in both CIDP and control samples (2/99 CIDPs and 2/100 controls for anti-EPHA7; and 2/100 CIDPs and 3/100 controls for ATP4A/4B). Samples positive for anti-ATP4A/4B showed reactivity against gastric parietal cells. Two CIDP patients had anti-LIF antibodies (2/99) while none of the control group (0/100) had. The same patients were positive in an anti-IFNL3 ELISA. One of these patients was also positive for anti-CASPR1. Both patients showed reactivity against human Schwann cells and large myelinating fibres of monkey peripheral nerve.

Conclusions:
Our work validates the utility of human cell microarray technology as a novel autoantibody-screening technology. Despite potential CIDP-associated autoantibodies (anti-LIF and anti-IFNL3) being identified, their clinical and pathogenic relevance to CIDP needs to be elucidated.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Antibodies, CIDP, Human cell microarray , Leukemia inhibitor factor, Inflammatory neuropathies

Peripheral T Helper CD4+ Cells Mediate Autoimmunity in Aire-deficient Model of Chronic Inflammatory Demyelinating Polyneuropathy

Poster No:
O 554

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Introduction:
Chronic inflammatory demyelinating polyneuropathy (CIDP) occurs spontaneously in NOD mice with Aire deficiency (NOD.AireGW/+). The disease is mainly driven by CD4+ cells. However, the contribution of different CD4+ T cell subsets to the pathogenicity of neuropathy is not well studied.

Methods:
The peripheral nerves, spleen and lymph nodes of NOD.AireGW/+ mice or NOD.WT mice assessed by single cell RNA sequencing (scRNA-seq) and flowcytometry. Adoptive transfer experiments performed on NOD.SCID mice as recipients. The severity of the neuropathy quantified by electromyography.

Results:
scRNA-seq of the immune cells infiltrating the sciatic nerves show that the majority of the CD4+ cells express genes associated with T follicular helper (Tfh) and T peripheral helper (Tph) cells, a newly described T helper type. Tph cells are similar to Tfh cells as they have prominent expression of ICOS, PD1, and IL-21. These IL-21+ Tph cells are also IFN-γ, IL-10 and CXCR6 positive, suggesting an effector phenotype. We verified high levels of IL-21 expression in Tfh and Tph cells in spleen and nerves by flow cytometry using IL-21 reporter mice. Transfer of CD4+ IL-21+ cells from NOD.AireGW/+ donor mice to immunodeficient mice resulted in higher neuropathy incidence than transfer of CD4+ IL21- cells. In adoptive transfer model, inhibition of Tfh specific transcription factor BCL6 decreased the frequency of Tfh and Tph cells in the peripheral nerves and protected against neuropathy development.

Conclusions:
IL-21 producing Tfh and Tph cells may play a major pathogenic role in neuropathy development and suggests new therapeutic targets for CIDP.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: CIDP, autoimmunity, T helper cells

Anti-Ganglioside (Complex) Antibodies In Patients From The International Guillain-Barré Syndrome Outcome Study

Poster No:
O 555

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Introduction:
Antibodies to various gangliosides (complexes) play a critical role in the pathogenesis of Guillain-Barré syndrome (GBS). Most previous studies investigated only a limited set of antibody specificities in a relatively small number of patients. Glyco-arrays provide the opportunity to determine clusters in a larger spectrum of specificities. In the current study we investigated the presence of anti-ganglioside (complex) antibodies in glyco-arrays in relation to the clinical characteristics, disease course, and outcomes in the first 1000 patients included in the International GBS Outcome Study (IGOS).

Methods:
Acute-phase sera from 762 GBS patients were tested for the presence of IgM, IgG and IgA against 16 glycolipids and all possible 1:1 complexes in glyco-arrays. Fluorescence intensities were clustered in heat maps per antibody isotype. Acquired patient clusters were analyzed in relation to clinical features.

Results:
Patients clustered into seven groups with distinct serum IgG antibody reactivity patterns: (1) GT1a complexes, (2) GT1a and GQ1b complexes, (3) GM1, GA1, and GD1b complexes, (4) GM1, GA1, GD1b, and additional GM1 complexes, (5) several GalNAc-GD1a complexes, (6) all GalNAc-GD1a complexes, and (7) one cluster with diverse specificities. Similar patterns were identified for IgM, although less evident. An additional IgM antibody reactivity cluster consisted of GM2 complexes. No cluster containing GQ1b complexes was found for IgM. IgA antibody reactivity patterns included four clusters of (1) GT1b, (2) SGPG, (3) GQ1b and GT1a, and (4) GalNac-GD1a complexes and three clusters with diverse specificities. The seven IgG clusters differed in Campylobacter jejuni and Mycoplasma pneumoniae positivity, frequency of clinical variants, Medical Research Council sum scores during follow-up, and the ability to walk unaided at 26 weeks.

Conclusions:
Various clusters of anti-ganglioside (complex) antibody reactivity were identified in GBS and were associated with clinical characteristics, disease course, and outcome. Further analyses into clinical associations will be presented at the PNS Meeting.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Guillain-Barré syndrome, Biomarkers, Anti-ganglioside antibodies, Prognosis

EAN/PNS Guideline On The Diagnosis And Treatment Of Guillain-Barré Syndrome (GBS)

Poster No:
O 556

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Introduction:
Guillain-Barré syndrome (GBS) is an acute severe polyneuropathy. Symptoms may largely vary greatly in presentation and severity. The aim was to develop an evidence-based international guideline on the diagnosis and treatment of GBS.

Methods:
A Task Force (TF) of the European Academy of Neurology (EAN) and the Peripheral Nerve Society (PNS) constructed 14 Population/Intervention/Comparison/Outcome questions (PICOs). Data were extracted and summarized in GRADE Summaries of Findings (for treatment PICOs) or Evidence Tables (for diagnostic and prognostic PICOs). Statements were prepared according to the GRADE Evidence-to-Decision (EtD) frameworks.

Results:
We conducted a systematic search and reached consensus for six diagnostic PICOs and the PICO on prognosis. For the seven intervention PICOs we used the GRADE method. For diagnosis, principal GPPs are: GBS is more likely if there is a history of recent diarrhea or respiratory infection; CSF examination is valuable, particularly if diagnostic uncertainty; anti-ganglioside antibody testing is of limited clinical value in most patients; electrodiagnostic testing is advised to support the diagnosis; MRI/ultrasound should be considered in atypical cases. For treatment, the TF recommends to start IVIg, or plasma exchange (PE) in GBS patients within 2 weeks after onset of weakness if unable to walk unaided. The TF

recommends against a second IVIg course in patients with a poor prognosis, or using corticosteroids; does not recommend PE followed by IVIg; weakly recommends some drugs for treatment of pain; does not recommend specific treatment for fatigue. The TF advises using the modified Erasmus GBS outcome score (mEGOS) to assess outcome, and the modified Erasmus GBS Respiratory Insufficiency Score (mEGRIS) to assess risk requiring artificial ventilation. Three NEW flowcharts are provided to assist making clinical decisions on the diagnosis, treatment, and the need for ICU admission.

Conclusions:
The final version of the EAN/PNS Guideline on the diagnosis and treatment of GBS is expected to be available at the PNS 2023 Meeting.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support: Peripheral Nerve Society (PNS) European Academy of Neurology (EAN) GBS/CIDP Foundation International GAIN Charity UK

Keywords: Guillain-Barré, Polyneuropathy, Guideline, Diagnosis, Treatment

Neuropathic Pain Consortium (NPC) Abstracts

O 557

Long Read Sequencing of Human Dorsal Root Ganglia Reveals Novel Isoforms

Poster No:
O 557

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Introduction:
Characterization of the transcriptome of the human peripheral nervous system is imperative to understand the mechanisms facilitating the sensation of pain, as well as the biomolecular changes underlying the development of chronic pain. Alternative splicing allows the generation of multiple isoforms from a single gene, affecting protein structure, as well as expression patterns, through inclusion and exclusion of whole or partial exons, phosphorylation sites, or binding sites for RNA-binding proteins. In this study, we used long read sequencing (LRS) on human dorsal root ganglia (hDRGs) recovered from organ donors to explore the diversity of transcripts and isoform expression in the peripheral nervous system. LRS provides novel insight into the transcriptome by producing full-length transcripts, thereby facilitating the identification of alternative splice sites and measurement of splice isoforms. In silico validation was carried out by confirming the expression of novel isoforms in short read sequencing data of hDRGs from different donors.

Methods:
LRS was performed on hDRGs from 3 donors and over 90,000 unique isoforms were identified following standard filtering criteria with 25,413 isoforms characterized as novel. Expression of novel isoforms was confirmed in hDRG from postmortem tissue donors by mapping short read sequencing data to the transcriptome generated through LRS.

Results:
Our study reveals the expression of isoforms using novel splice sites, including isoforms of the WNK1 gene which contain a previously unidentified exon. Alternative splicing of WNK1 in the nervous system has previously been associated with the development of neuropathic pain, indicating the functional implications of diversity in isoform usage.

Conclusions:
This is believed to be the first study to use LRS to characterize the hDRG. Our results show novel isoform expression patterns within the peripheral nervous system, highlighting the importance of characterizing novel splice site usage, and providing significant insight into the transcript diversity of the human peripheral nervous system.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Long read sequencing, Human dorsal root ganglia, Transcriptome, Isoforms, Alternative splicing

International Diabetes Neuropathy Consortium

International Diabetes Neuropathy Consortium (IDNC) Abstracts

O 558

Spatial Analysis of Human Dorsal Root Ganglia Reveals Transcriptomic Changes Associated with Diabetic Peripheral Neuropathy

Poster No:
O 558

Authors:
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Institutions:
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Introduction:
Diabetic peripheral neuropathy (DPN) is a prevalent complication of diabetes that causes nerve damage in the peripheral nervous system. DPN is associated with substantial morbidity including foot ulcers and lower limb amputation. Symptoms of DPN include pain, dysesthesias and numbness.

Methods:
In this study, we performed Visium spatial transcriptomics on dorsal root ganglia (DRGs) recovered from organ donors with a medical history of DPN. This approach provides near-single neuron resolution and allows the characterization of cell-cell interactions with spatial context. Our goal was to characterize any changes in neuronal subtypes and their profiles between DPN and healthy donors. We also aimed to profile non-neuronal cells (e.g., immune cells) and their interactions with neurons in DPN.

Results:
We identified more than 3000 barcodes that overlap single neurons and profiled their transcriptome. Our analysis revealed important changes in the transcriptome of neuronal subtypes in DRGs from DPN donors compared to healthy donors, particularly genes involved in inflammatory responses. Spatial analysis of the DRGs from DPN donors also showed the presence of immune cells such as T-cells and macrophages. These immune cells release factors that can interact with neurons and contribute to the symptoms associated with DPN.

Conclusions:
Overall, our study provides insights into the molecular changes that occur in DRGs in the context of DPN and identifies potential targets for therapeutic intervention. The identification of specific neuronal subtypes that are particularly affected in DPN may aid in the development of targeted treatments that could help alleviate the symptoms of this debilitating condition. Our findings also highlight the importance of using spatial transcriptomics in studying the molecular changes that occur in specific tissues and cell types in pathological conditions like peripheral neuropathies.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Diabetic neuropathy, DRG, Spatial sequencing

Inflammatory Neuropathy Consortium

Inflammatory Neuropathy Consortium (INC) Abstracts

O 559

A Prospective Open-label Trial with Rituximab in CIDP Patients not Responsive to Conventional Immune Therapies

Poster No:
O 559

Authors:
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Institutions:
[1]Milan University, IRCCS Humanitas Research Institute, Rozzano, Milan, Lombardia, [2]IRCCS Humanitas Research Hospital, Humanitas University, Milano, Italy, [3]Istituti Clinici Scientifici Maugeri, Torino, Italy, [4]Dipartimento di Neurologia, IRCCS San Raffaele, Milano, Italy, [5]IRCCS, Ospedale Policlinico San Martino, Genoa, Italy, [6]Presidio Sanitario Major, Istituti Clinici Scientifici Maugeri, Torino, Italy, [7]IRCCS Humanitas Research Hospital, Rozzano, Italy, [8]IRCCS San Raffaele Scientific Institute, Milan, Italy, [9]IRCCS Ospedale Policlinico San Martino, Genova, Italy, [10]IRCCS Humanitas Research Hospital, Milan, Italy, [11]IRCCS-Istituto Mario Negri, Milan, Italy

Introduction:
Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is a chronic immune-mediated neuropathy often responding to steroids, intravenous immunoglobulins or plasma exchange. These therapies needs to be continued for a long period of time to avoid patient deterioration. We evaluated the efficacy of rituximab in a prospective open-label study on patients with CIDP not responding to at least two conventional immune therapies.

Methods:
We performed and open-label prospective study with intravenous rituximab (1 gram, day 1 and 15) on 20 patients with CIDP not responsive to at least two conventional immune therapies. The primary end-point was the proportion of patients improved by at least one point on the INCAT scale or two points on MRC scale or four points on the RODs scale, 6 months after therapy with rituximab. Secondary endpoints included the proportion of patients improved 12 months after therapy; improved after 6 and 12 months in electrophysiological parameters; discontinued treatment with rituximab due to side effects or voluntary withdrew; improved the quality of life according to the SF-36 scale.

Results:
Twenty patients were enrolled in the study including one who retired the consent before treatment and two screening failure. Fourteen of the 17 treated patients (76.5%) had improved at 6-month, 10 if we considered 4 MRC points improvement (58.8%). Of the 14 patients completing the 12-month follow-up (two lost to follow-up after being improved at month 8 and 10, and one deteriorated at 6 month), 13 had improved at 12 month (92.9%), 10 considering 4 MRC points (71.4%). When we included missing data, 15/17 had improved (88.2%; 12/17, 70.6% with 4 MRC).In 7/17 treated patients (41.1%) nerve conduction parameters had improved by at least 20% in two nerves. None of the treated patients retired for side effects.

Conclusions:
Rituximab was a safe and effective therapy in patients with CIDP unresponsive to conventional therapies

References:
No

References 1:

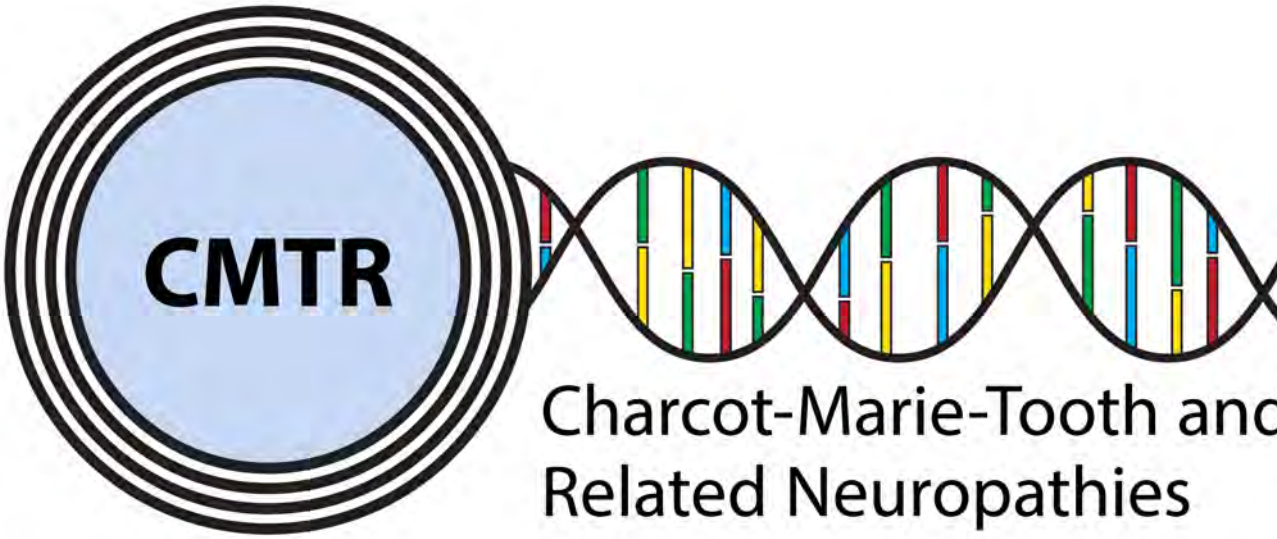
References 2:

References 3:

References 4:

Grant Support:

Keywords: Chronic inflammatory demyelinating polyradiculoneuropathy, Rituximab, Open-label prospective trial, CIDP



Charcot-Marie-Tooth and Related Neuropathies (CMTR) Abstracts

O 560-561

Overcoming Genetic Neuromuscular Diagnosis Pitfalls in a Middle-Income Country: Lessons Learned from a Transcontinental Consortium

Poster No:
O 560

Authors:
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Introduction:
Advancements in molecular diagnosis have provided valuable insights into rare diseases, allowing for improved standards of care. Despite this, access to genomic diagnosis remains limited in middle-income countries such as Brazil. In this context, we share our experiences in a transcontinental genomic consortium for neuromuscular disorders, highlighting how collaborative efforts have helped overcome various obstacles in diagnosing our patients.

Methods:
We present several cases categorized into three themes, highlighting significant gaps in genetic diagnosis: 1) reverse phenotyping and variant validation, 2) deep phenotyping and identification of the best molecular approach, and 3) exploration of genomic tests beyond whole exome sequencing (WES).

Results:
The importance of functional analysis is highlighted in the first group, where enzyme activity testing, muscle biopsy, and a model Xenopus system were used to validate variants in cases including GALC, POLG and KCNA1 variants. The second group emphasizes the necessity of deep phenotyping to guide genomic analysis, revealing a double hit genetic disorder in one case where a homozygous variant on IGHMBP2 gene was not enough to explain motor neuronopathy and joint hypermobility, leading to a second virtual panel analysis on WES, revealing another class 5 homozygous variant on ALDH18A1 gene. Finally, the need for alternative molecular approaches beyond WES is discussed in the third group, where a novel pipeline detected a biallelic deletion in SPG 11 gene, missed by WES; and recently described SCA 27b diagnosed through repeat expansion analysis in 6 out of 51 of our patients with late onset cerebellar ataxia.

Conclusions:
Our experience has shown that establishing a virtual transcontinental partnership is viable, as it offers valuable intellectual support, specialized training on a local level, and access to diverse molecular diagnosis strategies and functional analysis. Collaborative efforts such as these have the potential to

overcome local obstacles, strengthen scientific capabilities, foster diverse multi-ethnic cohorts, and ultimately provide improved care for patients.

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Yes

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References 2:
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References 3:
Robinson PN. Deep phenotyping for precision medicine. Hum Mutat. 2012 May;33(5):777-80. doi: 10.1002/humu.22080. PMID: 22504886

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Grant Support:

Keywords: International cooperation, Neurogenetics , Genomics, Deep phenotyping, Reverse phenotyping

Reticulon 2 (RTN2) Deficiency Leads to a Recessive Distal Motor Neuropathy with Spastic Paraplegia

Poster No:
O 561

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Introduction:
Heterozygous variants in reticulon 2 (RTN2) were linked to an early-onset and rapidly progressive subtype of hereditary spastic paraplegia (HSP) in a small group of patients (SPG12). Most of them were described to have a predominantly pure HSP phenotype.

Methods:
Using exome and genome sequencing we identified 12 individuals from 6 families with ultra-rare homozygous loss-of-function RTN2-variants. A homozygous C. elegans mutant strain, ret-1, containing LoF deletion of worm RTN2 ortholog, ret-1, was generated. Phenotypic differences in baseline morphology, posture and locomotion of ret-1, and differences in behaviour as the result of treatment with a panel of bioactive molecules were identified using high-resolution worm tracking coupled with automated behavioural phenotyping.

Results:
All individuals with homozygous RTN2-variants presented with slowly progressive paraspasticity in combination with distal motor neuropathy affecting the upper and lower limbs, with an early age of onset between 1 and 6 years. All patients had a slowly progressive disease course and remained ambulatory at the time of investigations. Nerve conduction studies confirmed axonal motor neuropathy with neurogenic changes in the myography. Characterisation of C. elegans RTN2 homolog loss-of-function mutants revealed morphological and behavioural differences compared to the parental strain. Treatment of the mutant with a sarcoplasmic reticulon Ca2+ reuptake inhibitor rescued key phenotypic differences.

Conclusions:
We delineate a new subtype of distal hereditary motor neuropathy with HSP features associated with RTN2 deficiency. Further, we identify the potential therapeutic benefit of inhibiting Ca2+ reuptake in the sarcoplasmic reticulon for the treatment of RTN2 disorders.

References:
No

References 1:

References 2:

References 3:

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Grant Support:

Keywords: RTN2, Homozygous variant, Distal hereditary motor neuropathy, Hereditary spastic paraplegia

Neuropathic Pain Consortium (NPC) Abstracts

O 562

A novel neuropathic pain treatment targeting Semaphorin 3E

Poster No:
O 562

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Institutions:
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Introduction:
Semaphorins (SEMAs) and their receptors, Plexins, are expressed in pain-conducting neurons of dorsal root ganglia (DRG). However, it remains unclear their association with neuropathic pain (NP). Herein, we aimed to clarify the association between NP and SEMA-Plexin pathway.

Methods:
We quantified serum SEMA3A, 3E, 4A, 4D, and 7A in 45 patients with NP and 17 age- and sex-matched healthy controls (HCs) by enzyme-linked immunosorbent assay (ELISA). SEMA expression in DRG and peripheral nerve (PN) tissues of 4 autopsied patients with NP and 2 controls as well as NP model mice with partial sciatic nerve ligation (PSL) was assessed by immunohistochemistry (IHC). Moreover, we intraperitoneally injected SEMA-blocking antibody or control IgG into NP model mice for 5 consecutive days after PSL, and assessed mechanical hypersensitivity using von Frey filament on day 4 after PSL. In vitro, we evaluated neurite outgrowth and the gene expression by RNA microarray analysis of mouse dissociated DRG neurons treated with or without SEMA3E.

Results:
Serum ELISA showed a significant increase of the SEMA3E, a ligand of Plexin D1, in patients with NP compared to HCs. IHC revealed enhanced SEMA3E expression in DRG and PN tissues of both NP patients and NP model mice, especially in macrophages. SEMA3E-blocking antibody injection not only abolished macrophage activation in sciatic nerves and DRGs but also resolved hypersensitivity in NP model mice. In vitro, SEMA3E treatment inhibited neurite outgrowth of DRG neurons. In RNA microarray analysis, DRG neurons treated with SEMA3E showed significant upregulation of S100A9 which promotes macrophage migration and downregulation of Dync1h1 and Faim2 that promote neurite outgrowth compared to non-treated DRG neurons.

Conclusions:
Our study suggests that SEMA3E upregulation in sensory nervous system was associated with NP via macrophage activation and inhibits regeneration of the injured nerve. The SEMA3E blockade could be a novel NP treatment.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: neuropathic pain, neuropathy, inflammation, nerve regeneration, immunity

International Diabetes Neuropathy Consortium

International Diabetes Neuropathy Consortium (IDNC) Abstracts

O 563

Comparative Diagnostic Characteristics Of Confocal Corneal Microscopy And Skin Biopsy for Neuropathy

Poster No:
O 563

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Institutions:
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Introduction:
Skin biopsy measuring nerve fiber density (NFD) is the best quantitative diagnostic test for small fiber neuropathy (SFN). Confocal corneal microscopy (CCM) is a less invasive potential alternative to skin biopsies, but the comparative performance with skin biopsy is unknown.

Methods:
Participants were recruited from bariatric surgery clinics with testing performed prior to surgery. SFN and distal symmetrical polyneuropathy (DSP) were defined according to the Toronto consensus definition of probable SFN and DSP respectively. Participants received CCM testing and 3mm punch skin biopsies of the distal leg and proximal thigh. Right and left CCM measurements were averaged including corneal nerve fiber density (CNFD), corneal nerve brand density (CNBD), corneal nerve fiber length (CNFL), and tortuosity coefficient (TC). We performed receiver operating characteristic curve analysis to assess classification of neuropathy using the area under the curve (AUC) for both SFN and DSP.

Results:
We recruited 140 patients with a mean (SD) age of 50.9 (7.1) years, BMI of 43.6 (28.5) kg/m2, and 77.1% were female. Distal leg NFD revealed an AUC of 0.85 (0.74- 0.96) for SNF and 0.78 (95% CI: 0.68-0.89) for DSP. Proximal thigh NFD demonstrated an AUC of 0.59 (0.46-0.73) for SFN and 0.59 (0.48-0.69) for DSP. CMM measurements had poor classification ability with AUCs for CNFD, CNBD, CNFL, and TC all $\leq$0.62 and $\leq$0.60 for SFN and DSP respectively. Participants did not have a preference for one procedure over the other (50.7% preferred skin biopsies and 49.3% preferred CCM).

Conclusions:
While CCM is less invasive than skin biopsy, the diagnostic characteristics of skin biopsy are much better than CCM for both SFN and DSP in obese patients. While the clinical role of these tests is unclear, research studies requiring quantitative testing of SFN should utilize skin biopsies of the distal leg.

References:
No

References 1:

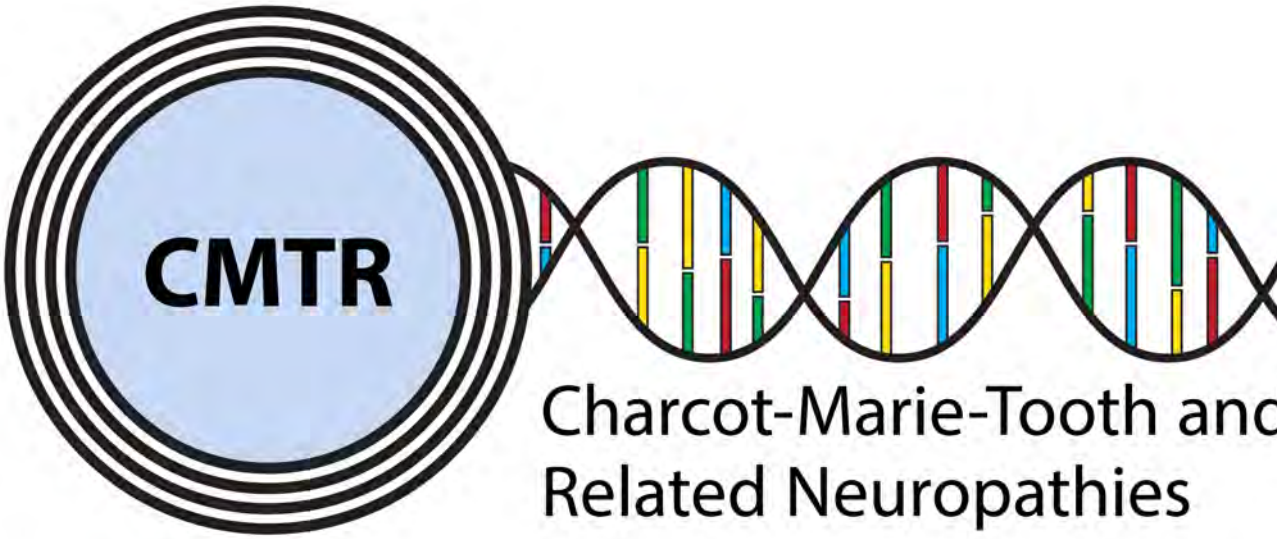
References 2:

References 3:

References 4:

Grant Support:

Keywords: Neuropathy, Obesity, NFD, SFN, CCM



Charcot-Marie-Tooth and Related Neuropathies (CMTR) Abstracts

O 564

ORY-4001, a Novel Potent and Selective Oxadiazole-Based HDAC6 Inhibitor Shows Pre-Clinical Therapeutic Efficacy in CMT1A

Poster No:
O 564

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Introduction:
Charcot-Marie-Tooth (CMT) is the most common form of inherited neuropathies affecting around 1 in 2500 individuals, who currently lack approved therapeutic options. The most common CMT subtype (CMT1A) is mainly caused by a duplication of the peripheral myelin protein 22 (PMP22) gene, leading to protein overexpression and aggregation, consequently decreasing the functional PMP22 being trafficked to the plasma membrane and ultimately resulting in demyelination of the peripheral axons. Histone Deacetylase 6 (HDAC6) inhibitors are emerging as a promising treatment option for CMT, as numerous studies have proven HDAC6 to be a key player in the regulation of both protein degradation pathways and axonal transport, and its inhibition reverted these dysregulated processes in CMT models. Herein we show the positive therapeutic effects of the novel potent and selective oxadiazole-based HDAC6 inhibitor, ORY-4001, in the C3 mouse model of CMT1A.

Methods:
8-week old C3-PMP22 transgenic mice (B6.Cg-Tg(PMP22)C3Fbas/J) were treated for 6 weeks (B.I.D, po) with ORY-4001. A mixture of baclofen/naltrexone/sorbitol was included as positive control of the study in the same administration scheme. Grip test, rotarod and sciatic nerve electrophysiology were measured at baseline and after treatment. Sciatic nerve histopathology was evaluated by toluidine blue staining at end-point.

Results:
ORY-4001 significantly increased nerve conduction velocity and compound muscle action potential resulting in improved neuromuscular strength and coordination. The treatment also produced a significant body weight gain. Sciatic nerve histopathology confirmed increased number of axons and improved myelination.

Conclusions:
ORY-4001 is a novel potent oxadiazole-based HDAC6 inhibitor with improved selectivity and safety profiles compared to hydroxamate-based HDAC6i. ORY-4001 improves both demyelination and axonopathy in the clinically relevant C3-PMP22 mouse model of CMT1A when administered as a therapeutic treatment to adult mice already displaying an overt CMT1A phenotype. Further studies with ORY-4001 are planned.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: CMT1A, HDAC6 inhibitor, Oxadiazole, PMP22, Animal model

Inflammatory Neuropathy Consortium

Inflammatory Neuropathy Consortium (INC) Abstracts

O 565

IgM anti-GM2 antibodies in patients with multifocal motor neuropathy target Schwann cells and are associated with early onset

Poster No:
O 565

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Institutions:
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Introduction:
Multifocal motor neuropathy (MMN) is a rare, chronic immune-mediated polyneuropathy characterized by asymmetric weakness mainly affecting distal limb muscles. MMN is associated with IgM antibodies against the ganglioside GM1, which are thought to activate complement at the nodes of Ranvier, disrupting axon-Schwann cell (SC) interactions. SCs express various gangliosides, including GM1 and GM2, but the role of SCs in MMN pathogenesis remains largely unknown. The goal of this study was to extend observations of the role of IgM antibodies against gangliosides in MMN pathogenesis, using a Schwann cell line (and iPSC-derived motor neuron (MN) model) and a cohort of 124 MMN patients.

Methods:
Cells were opsonized with MMN patient sera and IgM binding was compared between SCs and MNs. Complement activation was studied at multiple levels. We investigated ganglioside-specificity of the observed IgM binding using cell-based and ELISA-based systems. Clinical correlations with IgM anti-GM2 seropositivity were assessed.

Results:
Fourteen of 124 patients were positive for IgM anti-GM2. IgM binding to SCs correlated with IgM anti-GM2 antibody titers, but not with IgM anti-GM1 titers. IgM GM2 seropositive patients did not present increased IgM binding to MNs. Pre-treating anti-GM2 positive MMN serum with soluble GM1/GM2 indicated GM2 specificity. We observed a strong correlation between IgM anti-GM2 binding and complement activation on SCs, resulting in C3 fixation and C5a formation. Finally, IgM anti-GM2 positive patients had a significantly lower age of onset than patients with anti-GM1 antibodies or without detectable antibodies.

Conclusions:
We show that IgM anti-GM2 antibodies are found in 11% of patients with MMN, and that SCs are specifically targeted by these antibodies. Moreover, IgM anti-GM2 seropositivity is associated with an earlier disease onset. Our data suggest that, in a subgroup of patients, these antibodies contribute to the disease development and emphasize the potential role of SCs in MMN pathology.

References:
No

References 1:

References 2:

References 3:

References 4:

Grant Support:

Keywords: Multifocal motor neuropathy, Schwann cells, Complement, Anti-ganglioside antibodies, GM2